Boletín

VOL. 90 • NUM. 1 - 2 - 3 • ENERO - FEBRERO - MARZO 1998



ASOCIACION MEDICA de Puerto Rico

PLAZA LAS DELICIAS, PONCE
...FIA POR: DR. ANSELMO MIRANDA MARTIR

ASOCIACION MEDICA DE PUERTO RICO

BOLETIN

VOL. 90 • NUM. 1 - 2 - 3 • ENERO - FEBRERO - MARZO 1998

OFICINAS ADMINISTRATIVAS

Asociación Médica de Puerto Rico
Ave. Fernández Juncos Núm. 1305 • Apartado 9387
San Juan, Puerto Rico 00908 • Tel (787) 721-6969

SUBSCRIPCIONES Y ANUNCIOS

Asociación Médica de Puerto Rico
Apartado 9387 • San Juan, P.R. 00908 • Tel. (787) 721-6969

Publicación trimestral - $40.00 anuales. El Boletín se distribuye a todos los miembros de la Asociación Médica de Puerto Rico como parte de su cuota anual.
Todo anuncio que se publique en el Boletín de la Asociación Médica de Puerto Rico deberá cumplir con las normas establecidas por la Asociación Médica de Puerto Rico y la Asociación Médica Americana.
La Asociación Médica de Puerto Rico no se hace responsable por los productos o servicios anunciados. La publicación de los mismos no necesariamente implica el endoso de la Asociación Médica de Puerto Rico.
Todo anuncio para ser publicado debe reunir las normas establecidas por la publicación. Todo material debe entregarse listo para la imprenta y con sesenta días de anterioridad a su publicación. La AMPR no se hará responsable por material y/o artículos que no cumplan con estos requisitos.
Todo artículo recibido y/o publicado está sujeto a las normas y reglamentos de la Asociación Médica de Puerto Rico. Ningún artículo que haya sido previamente publicado será aceptado para esta publicación. La Asociación Médica de Puerto Rico no se hace responsable por las opiniones expresadas o puntos de vista vertidos por los autores, a menos que esta opinión esté claramente expresada y/o definida dentro del contexto del artículo.

Boletín de la Asociación Médica de Puerto Rico is published quarterly for $40.00 per year by Asociación Médica de Puerto Rico, 1305 Fernández Juncos Ave. P.O. Box 9387, San Juan, Puerto Rico 00908.
"POSTMASTER" Send address changes to Boletín Asociación Médica de Puerto Rico, 1305 Fernández Juncos Ave. P.O. Box 9387, San Juan, Puerto Rico 00908.

Catalogado en Cumulative Index e Index Medicus.
Listed in Cumulative Index and Index Medicus.
No. ISSN - 0004-4849

CONTENIDO



JUNTA DE DIRECTORES 1998

Gonzalo González Liboy, M.D.
Presidente

Luis A. Parés Martínez, M.D.	*Presidente Electo*
Jaime M. Díaz Hernández, M.D.	*Presidente Saliente*
Sylvia A. Fuertes Thomas, M.D.	*Secretaria*
José I. Iglesias, M.D.	*Tesorero*
Luis Aponte, M.D.	*Vicepresidente AMPR*
Roberto Rodríguez Martínez, M.D.	*Vicepresidente AMPR*
Carlos García Goyco, M.D.	*Vicepresidente AMPR*
Miguel A. Cubano, M.D.	*Pres. Cámara Delegados*
Eladio Santos Aponte, M.D.	*Vicepres. Cámara Delegados*
Filiberto Colón Rodríguez, M.D.	*Delegado AMA*
Emilio A. Arce, M.D.	*Delegado AMA*
Calixto E. Pérez Prado, M.D.	*Delegado Alterno AMA*
Antonio De Thomas, Jr., M.D.	*Delegado Alterno AMA*

PRESIDENTES DE DISTRITOS Y CONSEJOS

Héctor Hernández Ortega, M.D.	*Presidente Dtto. Noreste*
Luis H. Rodríguez García, M.D.	*Presidente Dtto. Sur*
Jerry Ramos Rodríguez, M.D.	*Presidente Dtto. Guayama*
Rafael Fernández Feliberti, M.D.	*Presidente Dtto. Este*
José Martí Núñez, M.D.	*Pres. Consejo Política Pública y Legislación*
Santiago N. Sallaberry, M.D.	*Pres. Consejo e Instituto EMC*
Alicia Feliberti, M.D.	*Pres. Consejo de Serv. Médicos*
Gerardo Sanz Ortega, M.D.	*Pres. Consejo Etico-Judicial*
Carlos Gadea Mora, M.D.	*Pres. Consejo de Salud Pública y Medicina Gubernamental*
Raúl G. Castellanos Bran, M.D.	*Pres. Consejo Relaciones y Servicios Públicos*
Verónica Rodríguez, M.D.	*Pres. Comité de Afiliación y Credenciales*
Juan G. Figueroa Longo, M.D.	*Pres. Comité Científico*
Pedro M. Mayol, M.D.	*Pres. Junta Editora Boletín*
Francisco Rivera Lizardi, M.D.	*Pres. Junta Editora Prensa Médica*
José C. Román De Jesús, M.D.	*Pres. Comité Historia, Cultura y Religión*
Luis A. López Sánchez, M.D.	*Pres. Comité Calidad Ambiental*
José A. Rodríguez Ruiz, M.D.	*Pres. Comité Medicare*
Judith Román, M.D.	*Pres. Comité de Enlace con los Estudiantes de Medicina*
Sara B. Lebrón de Sanz, M.D.	*Pres. Comité de Responsabilidad Profesional*
Valeriano Alicea Cruz, M.D.	*Pres. Comité Esp. Médicas*
Luis A. Izquierdo Mora, M.D.	*Pres. Comité Asesor del Presidente*
Ovidio Rodríguez, M.D.	*Pres. Comité Planes Prepagados*
Francisco E. Colón Ramos, M.D.	*Pres. Comité Calidad de Vida*
Humberto Lugo Vicente, M.D.	*Pres. Comité Internet*
José C. Román de Jesús, M.D.	*Pres. Comité de Enlace Interamericano*
José R. Villamil, M.D.	*Pres. Comité del Médico Impedido*
Ramón Cuevas Natal, M.D.	*Pres. Comité Premios Bohique*
Luis A. Parés Martínez, M.D.	*Pres. Comité de Convención*
Jorge Colón Vélez, M.D.	*Pres. Comité de Biblioteca*
José M. Torres Ramos, M.D.	*Pres. Clínicas Externas*



Jaime M. Díaz Hernández, M.D.	*Pres. Comité Act. Musicales*
Carlos García Goyco, M.D.	*Pres. Comité Reforma de Salud*
Julio Rivera Ilarraza, M.D.	*Pres. Comité de Enlace con Agencias Federales*

PRESIDENTES DE SECCIONES

Francisco de la Torre, M.D.	*Alergia e Inmunología Clínica*
Luis Cumming Carrero, M.D.	*Anestesiología*
Amarilis Silva, M.D.	*Cirugía de Manos*
Luis E. Iguina Mella, M.D.	*Cirugía General*
José Ismael Iglesias, M.D.	*Cirugía Plástica*
Alma Cruz Santana, M.D.	*Dermatología*
Carlos H. Ramírez Ronda, M.D.	*Infectología*
Dwight Santiago Pérez, M.D.	*Medicina Deportiva*
Alicia G. Feliberti, M.D.	*Medicina de Emergencia*
Jaime M. Díaz Hernández, M.D.	*Medicina de Familia*
Emma Lou Carreras, M.D.	*Fisiatría*
José J. Corcino, M.D.	*Hematología y Oncología*
Raúl G. Castellanos Bran, M.D.	*Medicina General*
Félix Matos, M.D.	*Medicina Industrial*
Sylvia A. Fuertes, M.D.	*Medicina Interna*
Ramón Figueroa Lebrón, M.D.	*Neumología*
Heriberto Acosta, M.D.	*Neurología*
Manuel Náter Orsini, M.D.	*Obstetricia y Ginecología*
Antolín Alvárez Pont, M.D.	*Oftalmología*
José Montañez Huertas, M.D.	*Ortopedia y Traumatología*
Mariano González Diez, M.D.	*Otolaringología, Cirugía de Cabeza y Cuello*
José L. Miranda, M.D.	*Patología*
Juan F. Jiménez, M.D.	*Pediatría*
Carmen Zoraida Sanz, M.D.	*Psiquiatría*
Julio Rojo, M.D.	*Radiología*

Editorial:

En esta edición del Boletín se ha invitado a los miembros de la facultad de la Escuela de Medicina de Ponce a contribuir artículos de interés a la clase médica de Puerto Rico. La calidad del producto se hace evidente y felicitamos a todos los autores por su esfuerzo y trabajo. Nos llama la atención la relevancia que tiene muchos de estos trabajo a los múltiples problemas de salud que tiene nuestro pueblo. La temática de la prevalencia de los tumores de piel en Puerto Rico y su posible relación con un incremento en la exposición solar ameritan nuestra evaluación en torno al grado de protección de nuestros pacientes a los rayos ultravioletas. Los trabajos del Dr. Yamamura que contribuyen al entendimiento de los procesos básicos inherentes a la progresión y resistencia a la infección del virus de la immunodeficiencia humana en Puerto Rico establece la posición de este Centro de investigación como uno a la vanguardia en torno a los avances mas relevantes del último año. En la sección de artículos especiales constatamos los esfuerzos de nuestros colegas de Ponce de estructurar la enseñanza y evaluación del proceso clínico a los estudiantes de medicina. Entendemos lo ardua y esencial de esta labor en la formación de la clase médica del futuro y los felicitamos.

La Junta Editorial del Boletín agradece la labor desinteresada de todos los revisores de estos artículos por su gestión de mejorar la calidad de nuestra revista.

Atentamente,

PEDRO M. MAYOL, MD
ROBERTO HUNTER MELLADO, MD

COMPARTIMOS LA PREOCUPACION DE QUE NUESTRAS ESCUELAS DE MEDICINA TIENEN EL RETO DE ADIESTRAR UNA GENERACION DE MEDICOS QUE RESPONDEN AL RETO DE UN NUEVO PARADIGMA EN LA PRESTACION DE SERVICIOS MEDICOS.

Mensaje:

"La Medicina Puertorriqueña ante el Umbral de un Nuevo Siglo"

Por: Gonzalo González Liboy M.D., FACP
Presidente AMPR

Transformación de la Medicina Puertorriqueña en el Siglo XX

La Asociación Médica de Puerto Rico en sus 95 años de existencia ha sido testigo fiel de la transformación de la medicina en Puerto Rico. Durante este siglo el concepto de la realidad de la medicina ha pasado paulatinamente, pero de una forma constante, de ser una medicina basada en gran parte en el arte de la práctica de la medicina, a un concepto basado en la ciencia y en la evidencia médica. Nuestra Asociación Médica de Puerto Rico ha sido el puntal que ha marcado la directriz de este proceso de transformación de la medicina del siglo xx. Es de gran importancia para todos nosotros conocer el pasado y la forma en que ha evolucionado la medicina en Puerto Rico para estar preparados para enfrentar el futuro.

Nuestra Asociación tiene a la disposición de nuestros médicos, estudiantes y público en general un compendio de historia de la medicina en nuestra página electrónica. Bajo la presidencia del Dr. Calixto E. Pérez Prado en el 1989, se publicó una edición especial del Boletín de la Asociación Médica de Puerto Rico enfocando nuestra historia. Bajo la presidencia del doctor Jaime M. Díaz Hernández se creó un documental histórico grabado en cinta magnética como documento y testigo fiel de la importancia que ha tenido, tiene y tendrá nuestra Asociación Médica.

Es de vital importancia el continuar recopilando datos históricos, trascendentales en el envolvimiento de nuestra Asociación Médica con la medicina en Puerto Rico, para futuras generaciones. Durante mi presidencia este año, habremos de continuar la recopilación de los datos históricos que han influido en la medicina en nuestra Isla.

La Epidemia de Descubrimientos

En la historia de la medicina hay un tema que se repite constantemente. Este tema recurrente es la relación entre eventos fortuitos y la captación de estos elementos por mentes vigilantes que han tenido la capacidad de aprovecharlos.

Nos vienen a la mente dos científicos y dos descubrimientos que se aplican fielmente a este concepto.



El primero, fue Luis Pasteur en 1854 y el otro, fue el bacteriólogo británico Alejandro Flemming en 1928. La historia de estos dos gigantes en el campo de los descubrimientos médicos es de todos ustedes conocida. Lo mismo sucede en el campo de la práctica médica. Tiene que haber una mente cultivada y dispuesta a recibir la semilla intelectual para poder captar indicios vanales o por lo menos así parecerían a las personas no dotadas de la capacidad de captación, y hacer de estos indicios una fuente de sabiduría para llegar a conclusiones clínicas universales.

Con los descubrimientos de Flemming y Pasteur se desarrolla una nueva era que marca los avances extraordinarios en el mundo de los milagros médicos. Desde el descubrimiento de agentes y métodos antibacteriales hasta el comportamiento submicroscópico molecular y a nivel genético exponiendo nuestros secretos biológicos más intrincados, los científicos han podido crear un sistema de ingeniería molecular, llegando hasta la configuración de productos biogenéticos. Se ha hecho más fácil el entendimiento del proceso microbiológico y fisiológico de nuestras estructuras celulares. Todo este proceso de conocimientos médicos tuvo su mayor auge en el 1950 con la demostración del doble espiral de la estructura del DNA por James Wattson y Francis Crick en el 1 953. Esto abrió la puerta del entendimiento fundamental del proceso biológico. Más adelante nos ayudó a descubrir y echar luz sobre los secretos escondidos dentro de la membrana celular. En cada una de las

200 variedades de células aprendimos el comportamiento biológico realizado a través de los 75 trillones de células que crecen y se dividen en nuestro organismo.

Instrumentos y equipos médicos para llegar al diagnóstico co-ayudaron a la explosión de descubrimientos que han habido durante los últimos lO a 20 años.

Todos estos descubrimientos científicos han influenciado el trabajo hecho a la cabecera del paciente por médicos que seguían practicando el arte y la ciencia de la medicina. La aplicación de toda esta gama de elementos biotecnológicos directamente para solucionar los problemas del paciente, a venido a ser en algunos casos no solamente lo normal en la prestación de los servicios si no la regla de oro. La falta de objetividad en estos estudios sofisticados de laboratorio, técnica de imágenes computarizadas y la aparente ciencia ficción de innovaciones mecánicas como en las bombas de pulmón corazón, marcapasos electrónicos, cirugía guiada por televisión y toda esta gama de magia clínica ha puesto en peligro la relación humana entre médico y paciente. Esta tecnología es más certera, confiable y menos especulativa. En un período de 20 años el arte de curar ha pasado de un optimismo simple y restrictivo como en los antibióticos, a una era de múltiples visiones como las tenemos en la época molecular.

Aspecto Económico, Social, Político y Legal

Como resultado de toda esta tecnología, hemos visto que la expectativa de supervivencia en el hombre y en la mujer ha aumentado. Toda esta tecnología se ve enfrentada cara a cara con los estilos de vida adversos. Estos están en contraposición con los avances hechos en el campo científico.

Toda esta tecnología no tiende a abaratar los servicios médicos. Ha habido un aumento exagerado en los costos. Tampoco tiene la medicina moderna una atención completa a los elementos importantes del cuidado médico en los últimos momentos de vida con las implicaciones sociales y biomédicas inherentes. Aunque la calidad de vida de la población envejeciente, que aumenta vertiginosamente, ha mejorado, la longevidad de éstos ha resaltado la necesidad de buscar formas de bregar más adecuadamente con las enfermedades degenerativas y los problemas comunes de los envejecientes. La gran prevalencia de la enfermedad de Alzheimer, como un ejemplo, ha sido solamente reconocida recientemente. Hemos tenido hasta un Presidente de los Estados Unidos sufriendo este mal, lo cual ha hecho que se de un ímpetu más grande en el reconocimiento y en la investigación de este elemento patológico; ahora es que se están buscando a través de esfuerzos intensos métodos para descubrir el origen y los marcadores diagnósticos para hacer posible la identificación de esta enfermedad y su tratamiento temprano.

Los elementos socio-políticos y legales que están afectando la relación médico-paciente, apuntan hacia la necesidad imperiosa de prestar atención a esta vertiente de la práctica, ya que su influencia está socavando activamente la relación entre el médico, el paciente y los familiares de estos pacientes.

Al principio de este siglo los derroteros por los que se encaminaban las decisiones médicas las dictaban los médicos. Los médicos fuimos perdiendo capacidad decisional cuando estructuras gubernamentales y legales entraron a formar parte de las decisiones que correspondían al médico, al paciente y sus familiares. Más adelante con el advenimiento de los planes prepagados y la incursión de la política en la práctica de la medicina, nuestro poder decisional, disminuyó aún más. Los médicos tenemos que recobrar el liderazgo en la medicina. Nuestra posición es especial al ser portadores de los elementos científicos básicos que rigen las alternativas diagnósticas y de tratamiento.

Papel del Médico y la Asociación Médica ante la Nuevas Fronteras de la Medicina

Cualquiera que sea la proyección de la supremacía diagnóstica que tenga el médico en estos días, hay varios elementos trágicos y dramáticos que se han desarrollado recientemente y que han socavado la fe en los científicos y médicos.

Hasta el 1980 la clase médica había proclamado una victoria casi total contra las infecciones. Entonces, surge el descubrimiento de pacientes jóvenes con capósis sarcoma en el área de San Francisco. A principio de la década de 1980 comienza a surgir una nueva plaga, el virus de la inmunodeficiencia adquirida. Esta hace tambalear las estructuras clásicas al enfrentarnos a una gran interrogante. No sabemos si aún con los descubrimientos que se han hecho en la guerra a muerte contra esta plaga, podrá dicha batalla ser completamente ganada por el hombre.

Es aquí donde la posición del médico y la relación médico-paciente debe erguirse en forma vertiginosa para demostrar nuestra capacidad como sanador. En el caso del virus de VIH, la solución y la eliminación de esta plaga es tan simple que a veces pasa de manera desapercibida sin percatarnos que la eliminación de este nuevo ente patológico puede ser obtenida a través de la prevención.

Debido a que muchas veces nos enfocamos en los elementos esotéricos para solucionar los problemas médicos de nuestra sociedad, no nos percatamos que

(Continúa en la pág. 4)

frente a nosotros tenemos el arma más fuerte para combatir todos estos problemas epidémicos. En el cáncer del pulmón, la eliminación del cigarrillo es fundamental para eliminar casi del todo esta enfermedad. En lo que toca a las enfermedades cardiovasculares, elementos tan simple como el ejercicio y una dieta balanceada son fundamentales para evitar gastos gigantescos y una morbilidad desastrosa.

Teniendo Puerto Rico la incidencia más grande de diabetes entre los grupos étnicos de la nación norteamericana, es hora que comencemos a trabajar en la eliminación de factores de riesgo, tan sencillos como el ejercicio y la dieta como bases fundamentales para evitar su progresión. En la clínica, el evaluar en cada visita los pies de los pacientes diabéticos sería suficiente para evitar una serie de amputaciones costosas y detrimen-tales social y moralmente.

Todavía quedan muchas interrogantes en el campo de la medicina, estamos confiados que en el campo de la salud mental se harán muchos progresos durante los próximos años. Muchos de los problemas que no están resueltos ahora, posiblemente dentro de 10 a 15 años tendrán solución.

La gran proliferación de pseudo-científicos se debe única y exclusivamente a la morosidad de la clase médica a tomar las riendas dentro de la educación médica y no permitir que charlatanes utilizando los servicios de comunicación masiva lleven información fraudulenta, equívoca y crasamente errónea a nuestros pacientes.

Como al principio de este siglo, tenemos el conocimiento en nuestras manos. Depende de nosotros utilizarlo para el beneficio de nuestros pacientes. No debemos permitir que intereses económicos sean el único medio de divulgación de medidas preventivas. No permitamos que mercaderes del sufrimiento y la salud humana, portavoces de ideas descabelladas sean los paladines de la salud. Toca a nosotros los médicos orientar y educar.

En conclusión, durante nuestro año de Presidencia en la Asociación Médica habremos de enfatizar la educación como puntal directriz, no solamente a nuestros médicos si no que también a nuestros pacientes. Este Boletín es el ejemplo más clásico de ese propósito fundamental de esta Asociación Médica de Puerto Rico a través de sus 95 años de vida.

Nuestro lema para este año "Educación y Servicio para la Clase Médica y los Pacientes a través de la Asociación Médica de Puerto Rico."

FE DE ERRATA:

En el VOL. 89 NUM. 10-11-12, OCTUBRE, NOVIEMBRE, DICIEMBRE 1997 por error involuntario se publicó:

Fotografía: Anselmo Ramírez cuando debió ser:
Anselmo Miranda Martir, M.D.

En el artículo titulado: **"Brief Report: Successful extension of the transplant renal vein with a synthetic vascular graft"**; por error involuntario se omitió el nombre del autor;

Eduardo Santiago Delpín, MD

Mensaje Especial:

Quo Vadis ¿A dónde se dirige la educación médica a finales del siglo XX?

Jaime Rivera Dueño, M.D.
Presidente y Decano - Escuela de Medicina de Ponce

Una mirada retrospectiva a lo que ha venido ocurriendo con la enseñanza médica durante las últimas décadas, nos confirma que hemos estado en un constante y confuso período de transición que no parece tener fin. Múltiples factores parecen impactar e impedir que ocurra un período de estabilidad. Entre otros factores podemos señalar el cambio de una práctica predominantemente especializada a una primaria, el cambio de lidiar con una patología de enfermedades crónicas a una relacionada con nuevos estilos de vida, y los dramáticos avances tecnológicos que impactan todos los aspectos de la práctica médica y las nuevas formas de enseñanza.

Estos y otros factores requieren profundidad en su análisis para poder definir a donde vamos. Pero las experiencias que ya estamos viviendo están estableciendo las características del perfil de ese nuevo médico del futuro.

En estas pasadas décadas de turbulencia, la imagen del médico ha sufrido grandes cambios que se manifiestan en la percepción del pueblo que ahora lo describe como tecnócrata, deshumanizado, arrogante, interesado solo en lo económico y distanciado del dolor humano.

Estas percepciones que cada día se hacen más manifiestas en las encuestas de opinión pública, han llevado a las autoridades académicas a autoevaluarse para ver donde han fallado y a considerar las medidas que deben tomarse para lograr un cambio efectivo. A esos efectos ya hay un sinnúmero de Escuelas que están introduciendo cambios casi dramáticos en sus currículos orientados a la formación de un nuevo médico, más humanista, con una visión bio-sico-social, con una sensibilidad a los problemas comunitarios, con un dominio del arte de la práctica médica sobre estrictamente la tecnología y un respeto al dolor y la espiritualidad de los seres humanos. Esa parece ser y debe ser la visión del nuevo médico.

¿Quo Vadis? Quizás, paradójicamente, a volver a formar el tipo de médico que décadas atrás le dio tanta credibilidad y confianza a su profesión.

El Boletín y su Historia:

Nuestra opinión acerca de
"La medicina entre los indios"

Editorial Boletín Asociación Médica de Puerto Rico - Octubre 1904

Por el Dr. C. Coll y Toste

El último trabajo de nuestro distinguido amigo el doctor Stahl se titula *La medicina entre los indios.* Lo ha publicado en este Boletín de la Asociación Médica de Puerto Rico y ocupa los números comprendidos desde el 11 al 21.

Felicitamos al compañero por su labor de investigación histórica, aunque emita algunas opiniones con las cuales no estamos de acuerdo. Estas son las que vamos a someter al criterio de una sana crítica.

El hombre, en todos los países del mundo, hasta que no llegó a formar sociedades no se ocupó de la medicina. En las fases primeras de la evolución social alboreó la idea de la alianza ofensiva y defensiva. La presión de la necesidad forzó a los salvajes a agruparse para defender sus personas e intereses. En las primeras hordas humanas el más robusto y valiente dirigió la agrupación. La lucha por la existencia obligó a estos grupos a tener cierta organización para dirigir el combate y surgió entonces el jefe. Este fue también el más fuerte y el más hábil. De este progreso de confederación nació *la tribu* o *clann.* Nosotros usamos más el vocablo tribu de origen latino, *tribus,* que el de clan, de origen celta, *clann.*

Teniendo la *tribu* tenemos ya un principio de unidad social, aunque la consanguinidad es confusa aún, el matrimonio una promiscuidad reglamentada, la propiedad de las armas puramente personal, las que se inhumaban, quemaban o enterraban con el individuo. La vida completamente nómada. En este estado errabundo el hombre no se ocupó más que de curar sus heridas, y cuando estaba enfermo por causas naturales quedaba entregado a sus propios esfuerzos, separado del clann, o rematado,a excepción del jefe.

La tribu asentada, aparece el médico-augur. El hombre primitivo de todos los pueblos ha considerado las enfermedades como enviadas por un poder sobre natural; pero ligado a la naturaleza. Hay necesidad de aplacar la divinidad ofendida. De donde nace la idea de hermanar y fundir en una sola las dos facultades, la del médico y la del sacerdote. Los viajeros modernos nos lo testifican. Taylor asegura que en Nueva Zelanda hay la creencia, que cada enfermedad es producida por un dios particular. Entre los egipcios, los sacerdotes practicaban la medicina. Los romanos tenían en el Palatino un altar, en cuyas aras se procuraba conjurar la fatal influencia de la *malaria* con plegarias y ofrendas. Para los latinos la fiebre era el dios *Februus,* a quien estaba consagrado el mes de febrero, durante el cual se hacían sacrificios purificadores. Los griegos tenían la creencia, que irritado Júpiter contra Prometeo, por haber sustraído el fuego del cielo para

(Continúa en la pág. 7)

El Boletín y su Historia:

dárselo a los mortales, creó la diosa Pandora, la cual abrió la caja donde se ocultaban mil males, los que se diseminaron por el mundo, con regocijo de los dioses. También consideraban a la peste como enfermedad divina. (1) Podríamos multiplicar las citas. A pesar de perfeccionarse y civilizarse las sociedades, la creencia del origen divino de las enfermedades ha persistido bajo distintas formas.

Fue aquí, por lo tanto, explicado lo natural que era el tener nuestros indígenas sus médico-sacerdotes; hallándose este pueblo en el período social de la *piedra pulimentada*, o hablando con más propiedad paleontológica, en el período *neolítico* de la edad de la piedra.

El primer error del doctor Stahl, en su interesante trabajo, es llamar a estos médico-sacerdotes indo-antillanos *buhitís*.

El sabio amigo comete este *lapsus*, porque al escribir el vocablo sigue a Oviedo en su historia general de Indias. Cuando el célebre cronista vino a vivir a La Española (Santo Domingo), existían muy pocos indios quisqueyanos, y suprimidos sus usos y costumbres. Escribió sobre estos asuntos de *auditu*. Por eso, al consignar nombres indígenas comete muchos errores.

Fray Iñigo Abad, en su Historial de Puerto Rico, siguiendo las huellas de Oviedo, escribe también buhitís. Pedro Mártir de Angleria, más disparatero aun que Oviedo en filología indo-antillana, anota *bovitus*, en la Carta, CXC, a los obispos de Praga y Pamplona, *y boicios* en cl cap. VI, lb IX de su Primera Década Oceánica. Brau (2) también incurre en error escribiendo boitís, procurando hermanar la radical *bo* del vocablo con Pedro Mártir, en lo cual estuvo acertado; y siguiendo en la terminación de la palabra a Oviedo, en lo cual erró. Además, Brau suprime la letra *h* entre las vocales *o* é *i*, lo cual constituye otro error. La *h* puesta por los cronitas en palabras indo-antillanas tiene su valor fonético, lo mismo al principio del vocablo que interpuesta en él, aunque nosotros, hoy día, no la pronunciemos. El valor fonético de la *h* era una aspiración, como entre los árabes, parecido a la *j* unas veces, y otras a la *y* griega. En la carta de Cristóbal Colón escrita en el mar cuando regresaba del primer viaje, y enviada desde Lisboa, en Marzo de 1493 a Barcelona, donde se encontraban los Reyes Católicos, (3) se lee: "A la primera isla que yo fallé puse nombre San Salvador, a conmemoración de su Alta Majestad, el cual maravillosamente todo esto ha dado: los Indios la llaman Guanayaní". Después se ha escrito siempre por los cronistas Guanahaní. Véase por la cita que Colón trató de fijar con la y griega la aspiración india. Aún conservamos los vocablos indo-antillanos bohío, dahao, bihao, duho, pitahaya, que se pronuncian bojío, bijao, dajao, dujo y pitajaya.

Rochefort ha escrito Boyez. El Sr. Vidal Morales, en su Historia de Cuba (4) escribe Behique. Así lo escribió Herrera. El verdadero nombre del médico-sacerdote indo-antillano, era Bohique, como lo escribe Las Casas en la página 436 del tomo V de su Historia general de las Indias, aunque algunas otras partes de este autor se escriba el vocablo con be en lugar de bo. Bachiller y Morales estuvo muy acertado en su Cuba primitiva, pág. 215, al decir, "acaso sea Bohique el genuino nombre". Y lo mismo Rafinesque al anotar también Bohique.

Editorial: Boletín Asociación Médica de Puerto Rico
Volumen 2, No. 22, Octubre 1904

Estudios Originales:

Epidemiological trends of melanoma in Puerto Rico from 1975-1991

By: Jaime L. Matta, Ph.D., Cruz M. Nazario, Ph.D., Roy A. Armstrong, Ph. D. and Juan Navas, B. S.

Abstract: The purpose of this study was to determine the crude and age-adjusted incidence rates of melanoma for residents of Puerto Rico from 1975 to 1991. This is part of an ongoing NASA study aimed at estimating whether melanoma and cataracts have increased in Puerto Rico since 1978 because of potential stratospheric ozone depletion and increased ultraviolet-B (UV-B) radiation. Calculating the percent change from their lowest values in 1978 to 1991, the age-adjusted incidence rate of melanoma increased 528% for males and 200% for females in 13 years.

Introduction

Skin cancers are the most common types of human cancers, with about 500,000 new cases diagnosed annually in the United States (Scotto et *al.* 1982). The incidence of various types of skin cancer is increasing in epidemic proportions (DeVita et *al.* 1997.) Cutaneous melanomas are cancers of the pigment cells of the skin. Their incidence is about 10 times lower that of non-melanoma skin cancers (basal and squamous cell carcinomas). Cutaneous melanoma is becoming a more common disease (Balch et *al.* 1997). In 1995, an estimated 32,100 individuals developed melanoma and 7,200 died of the disease in the United States. In 1996, it was estimated that 38,300 new cases were diagnosed, a 12% increase in the incidence of the disease from 1995. No other tumor is increasing faster in number of new cases diagnosed (Balch et *al.*1997). Since 1950, the incidence of melanoma in the United States has increased steadily by 6% per year and the mortality rate by 2% per year. In the older caucasian population, the death rate for melanoma has doubled in the last 35 years with increases of approximately 5% per year. In the United States, twelve women and seven men die each day of melanoma and $1.25 billion is spent each year on the care of the melanoma patient. (Balch et *al.* 1997). Few studies (Vázquez-Botet et *al.* 1983; Vázquez-Botet et *al.* 1990) have been published with regards to the yearly trends in skin cancer incidence for residents of Puerto Rico.

Solar ultraviolet (UV) radiation is a potent environmental DNA-damaging agent and an inducer of skin cancer (DeVita et *al.* 1997). There is extensive evidence that chronic repeated exposure to solar UV is the primary cause of basal and squamous cell (non-melanoma) skin cancers (Rundel and Nachtwey 1978, Epstein 1983, Sober 1987, Swerdlow et *al.* 1988, Roza et *al.* 1989). Data establishing a direct causal relationship between malignant melanoma and exposure to sunlight are more complex but suggest a promotional role of sunlight in the cause of melanoma (DeVita et *al.* 1997). However, of the various health-related consequences of enhanced exposure to UV radiation, non-melanoma provide the most firmly established link between UV exposure and biological consequences (Lloyd 1993). They occur mostly in light skin people, and then predominantly on skin areas most exposed to sunlight, such as the face.

Methods

All of the data on melanoma utilized in this study was obtained from the Annual Reports of the Central Cancer Registry of the Department of Health of Puerto Rico. Basal and squamous cell carcinomas (non-melanoma) were excluded. The International Classification of Diseases for Oncology (I.C.D.O.) 173-(0-9) was utilized to identify melanoma cancer cases. Crude incidence rates were determined using the new cases divided by the corresponding group population and multiplying by 100,000. Age adjusted incidence rates was calculated based on the 1950 population. By adjusting the incidence rates to the 1950 Puerto Rican population we have mathematically removed the effect of the differences in the age distribution of the population in these time periods. This method produces a standardized rate for which the aging effect of the population and the effect it produces on cancer rates are moved. Thus, we can evaluate the trend in malignant melanoma as it correlates with potential risk factors other than age. The selection of this time period for adjustment, which is an arbitrary decision, does not affect the trends in the estimated cancer

Ponce School of Medicine, PO Box 7004 Ponce, PR 00732

incidence rates. The adjusted rate was obtained from the total expected cases divided by the total group population and multiplied by 100,000. The Central Cancer Registry published incidence rates for melanoma adjusted to the 1950 population until 1986, afterwards the referenced population in the annual reports was the 1970 population.

Results

In 1975, 88 new malignant melanoma cases were reported to the Puerto Rico Cancer Registry, 45 were diagnosed in males. In 1991, a total of 194 new melanoma cases were diagnosed, 121 of them diagnosed in Puerto Rican males, as shown in Table 1. The age-adjusted melanoma incidence rates in Puerto Rico by gender from 1975 to 1991 are shown in Figure 1. These varied from 0.7 in 1978, the lowest incidence rate in the study period to 4.4 per 100,000 in 1991 for males. For males and females a decreasing trend was observed from 1975 to 1978. However, from 1978 until 1991, the latest available data on cancer in Puerto Rico, an increasing trend in melanoma is evident (Figure 1). Puerto Rican males experienced 6.3 times the risk of being diagnosed with malignant melanoma in 1991 compared to their risk in 1978. For Puerto Rican females the relative risk was 3 times higher. After 1979, an excess risk of melanoma is observed for males compared to females during the same calendar year, excluding 1985 rates. In 1991, the male: female risk ratio was 2.1:1.0.

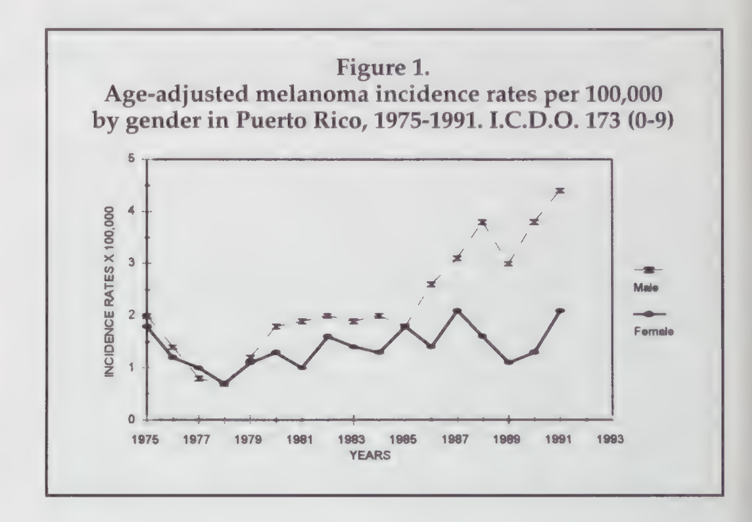


Figure 1.
Age-adjusted melanoma incidence rates per 100,000 by gender in Puerto Rico, 1975-1991. I.C.D.O. 173 (0-9)

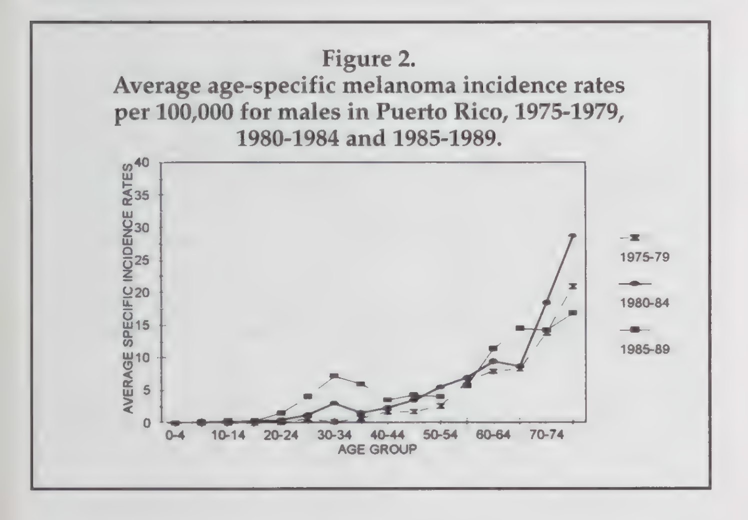
The average specific melanoma incidence rates by age group and gender are shown in Figures 2 and 3 for the 1975-1979, 1980-1984 and 1985-1989 quinquennia. Melanoma is a rare occurrence before age 20. An increasing risk with increasing age is

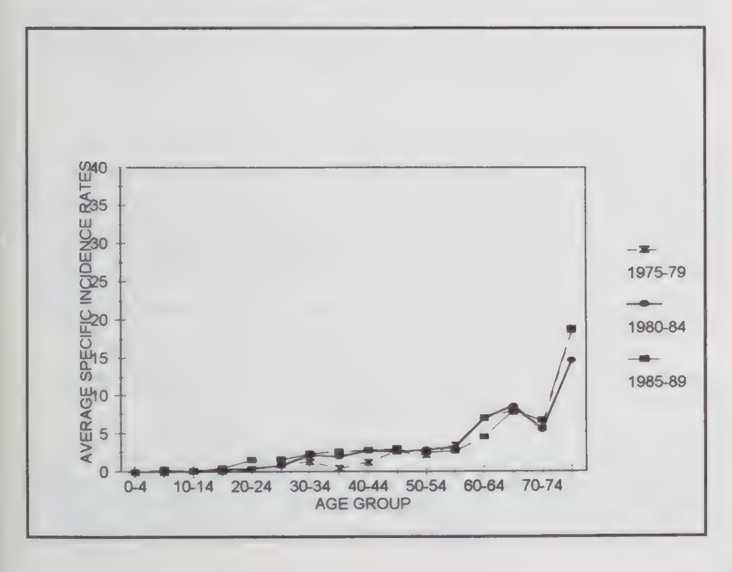
Table 1.
Malignant melanoma cases in Puerto Rico, crude and age-adjusted incidence rate for gender by year from 1975-1991.

Calendar Years	No. of Melanoma Cases - Male I.C.D.O. 173 (0-9)	Incidence Rate per 100,000		No. of Melanoma Cases - Female I.C.D.O. 173 (0-9)	Incidence Rate per 100,000	
		Crude Rate	Age Adjusted		Crude Rate	Age-Adjusted
1975	45	2.9	2.0	43	2.7	1.8
1976	34	2.2	1.4	28	1.7	1.2
1977	20	1.2	0.8	23	1.4	1.0
1978	18	1.1	0.7	17	1.0	0.7
1979	29	1.9	1.2	27	1.7	1.1
1980	42	2.7	1.8	31	1.9	1.3
1981	43	2.7	1.9	27	1.6	1.0
1982	53	3.3	2.0	42	2.5	1.6
1983	48	3.0	1.9	36	2.1	1.4
1984	50	3.1	2.0	31	1.8	1.3
1985	49	3.1	1.8	52	3.1	1.8
1986	55	3.5	2.6	43	2.5	1.4
1987	80	5.0	3.1	60	3.5	2.1
1988	73	4.6	3.8	43	2.5	1.6
1989	79	4.7	3.0	37	2.0	1.1
1990	102	6.0	3.8	43	2.4	1.3
1991	121	7.0	4.4	73	4.0	2.1

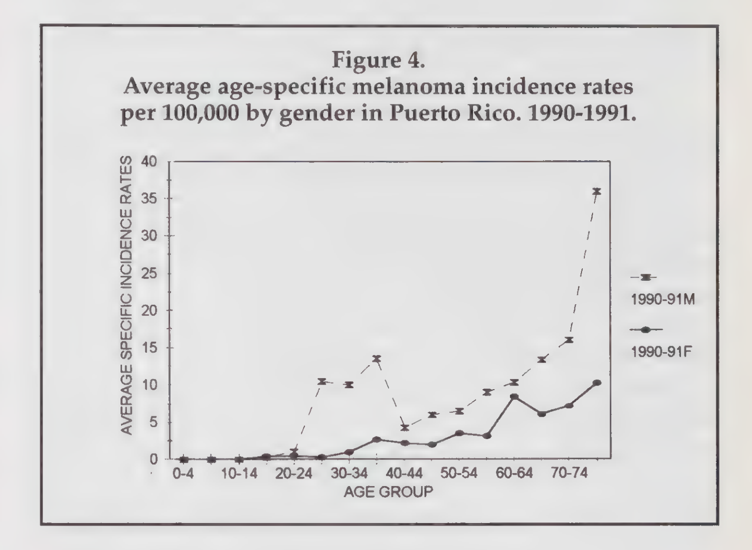
observed for males with an apparent peak at 30-34 years of age, discernible at latter calendar years (Figure 2). This peak is not conspicuous for females (Figure 3). Puerto Rican males 30-34 years of age had 40 times higher risk of developing malignant melanoma during the 1985-89 time period compared to males 30-34 years of age during the 1975-1979 quinquennium. But this large excess of risk was not observed when other age groups were compared. For example, Puerto Rican male's 40-44 years of age had twice the risk of developing melanoma during the later time period (1985-1989) as compared to the risk during 1975-1979. Therefore, prudence is recommended before making inferences regarding this data since the rates are based on very small numbers.

The risk of malignant melanoma increases with age in Puerto Rican females (Figure 3). The relative risk of malignant melanoma for a women over 75 years of age is about 20 times the risk of a women 25-29 years of age during the same time calendar period. In 1985-1989, the relative risk of female's 40-44 years of age was 2.8 times higher than the risk for women of the same age during the period between 1975-1979.


Figure 2.
Average age-specific melanoma incidence rates per 100,000 for males in Puerto Rico, 1975-1979, 1980-1984 and 1985-1989.



The observed trend of increasing risk with increasing age is also evident in Figure 4. During the 1990-1991 time period, melanoma incidence rate increased from 10.1 for males 30-34 years age to 36.2 per 100,000 for males over 75 years of age: a percent change of +258%. For females, the incidence rates increased from 1.5 (30-34 years of age) to 15.4 per 100,000 for females over 75 years of age: a percent change of +926%. The incidence rates for this time period are based on small numbers.


Figure 4.
Average age-specific melanoma incidence rates per 100,000 by gender in Puerto Rico. 1990-1991.

Discussion

Since 1950, in the United States the incidence rate of melanoma has increased steadily by 6% per year, and the mortality by 2% per year (DeVita et *al.* 1997). The 1983-1987 average annual age-adjusted incidence rates per 100,000 (adjusted to the world population) was 10.8 for White males, 8.8 for White females, 0.4 for Black males, 0.6 for Black females (Parkins et *al.* 1992).

This is the first epidemiological analysis of malignant melanoma that evaluates the trend of age-adjusted incidence rates (1950 Puerto Rican population) from 1975 to 1991 in Puerto Rico. From 1978 to 1991, the annual age-adjusted incidence rate for males increased an average of 0.5 for males and 0.23 for females. Puerto Rican males had twice the risk of females to develop melanoma and there is an apparent excess risk for males 30-34 years of age. The age and cohort effects are evident when age specific incidence rates are compared by quinquennium, the age effect being stronger. The results gathered support the hypothesis established in the cancer scientific literature concerning the correlation between the increased incidence of skin cancer (e.g. melanoma) as a function of increasing age. The data also suggests, that generally, males had a higher incidence of skin cancer than females in Puerto Rico during the study period. This higher incidence in males could be related to occupational exposure. Certain occupations in Puerto

Rico (e.g. fishermen, farmers, construction workers, athletes) are more likely to have a higher frequency of male workers. Workers in these occupations are exposed to higher doses of ultraviolet radiation when compared to office workers.

As part of an ongoing collaborative study between Ponce School of Medicine and the University of Puerto Rico, Mayaguez, an effort is being made to utilize satellite measurements of ozone levels between 1978-1997 in Puerto Rico in order to establish the relationship between stratospheric ozone and UV-B radiation obtained from the permanent UV monitoring station at the University of Puerto Rico (La Parguera). This relationship will enable us to estimate historical levels of surface UV-B radiation in Puerto Rico starting in 1978 and to estimate whether stratospheric ozone concentration and ground UV-B are linked to the increased incidence of melanoma reported in this study from 1978 to 1991. The ozone layer in the stratosphere serves as a highly effective absorbing layer that prevents the most biologically potent wavelengths of ultraviolet radiation, particularly UV-B (280-320 nm) from reaching the earth and exposing the human population (Hall 1997). Any increase in the penetration of UV-B resulting from a depletion of the ozone layer might be expected to increase the incidence of skin cancer, especially basal and squamous cell carcinomas (van der Leun and de Grujil 1993). It is estimated that a 1% decrease in ozone yields a 1.56% increase in carcinogenic UV, which in turn may lead to a 2.7% increase in non-melanoma skin cancer (van der Leun and de Grujil 1993).

The reason(s) for the nearly epidemic increase in the incidence of melanoma are still unclear, but may result from combinations of increased recreational exposure to sunlight, an increased amount of UV-B radiation from sunlight that reaches the earth's surface, and earlier detection of melanoma (Balch et *al.* 1997). Epidemiological studies indicate that skin cancers are most frequent at low latitudes, in outdoor workers, on exposed regions of the body, an in light-skinned individuals with blonde or red hair who have a tendency to burn rather than tan (Brash 1997).

In view of the possibiliy of increasing UV-B doses due to ozone depletion and/or as a result of changes in social habits (e.g. increased outdoor recreation, tanning salons), programs in many countries currently educate the public on safe sun exposure on the assumption that excessive exposure to natural ultraviolet radiation is the most important causative agent in developing malignant melanoma (Balch et *al.* 1997). Considering the sharp increases in the incidence of melanoma and that many residents in Puerto Rico are exposed to high levels of sunlight throughout the year an integrated approach towards the primary prevention of malignant melanoma should be evaluated by physicians, educators and health care workers in Puerto Rico.

Acknowledgements

These studies were supported by the National Aeronautics and Space Administration (NASA), Ames Research Laboratories, Office of Equal Opportunity Programs (OEOP) grant NAG 2-1149 to J.M. and R.A. The authors also wish to acknowledge the epidemiological expertise of Dr. Manuel Bayona, NOVA Southeastern University, the secretarial assistance of Mrs. Hannia Delgado, Ponce School of Medicine, and the cooperation of Dr. Diego Zavala, Director, Central Registry of Cancer.

References

Balch, C.M., Reintgen, D.S., Kirkwood, J.M., Houghton, A., Peters, L. and K. Kian Ang. 1997. In: **Cancer Principles & Practice of Oncology,** Fifth Edition, DeVita, V.T., Hellman, S., Rosenberg, S.A. Eds., Lippincott-Raven Publishers, 1997, 1947-1994.

Brash, D.E. Cancer of the skin. In: **Cancer Principles & Practice of Oncology,** Fifth Edition, DeVita, v.T., Hellman, S., Rosenberg, S.A. Eds., Lippincott-Raven Publishers, 1997, 1879-1933.

Cancer in Puerto Rico, Central Registry of Cancer, Dept. of Health, Commonwealth of Puerto Rico, Annual Reports from 1975 to 1991.

DeVita, V.T., Hellman, S. and S.A. Rosenberg. **Cancer: Principles & Practice of Oncology,** 5th edition, Lippincott-Raven Publishers, 1997, 3125 pp.

Epstein J.H. Photocarcinogenesis, skin cancer, and aging. J. Am. Acad. Dermatol., 1983;9:487-502.

Hall, E.J. Etiology of cancer:physical factors. In: **Cancer Principles & Practice of Oncology,** Fifth Edition, DeVita, V.T., Hellman, S., Rosenberg, S.A. Eds., Lippincott Raven Publishers, 1997, 203-210.

Lloyd, S.A. Stratospheric Ozone Depletion. The Lancet, 1993; 342: 1156-1158.

Parkin, D.M., Muir, C.S., Whelan, S.L., Gao, Y.T., Ferlay, F., Powell, J. Cancer incidence in five continents, 1992, vol. 6. IARC Scientific Publication no.120, Lyon.

Roza L., Baan, R. A., van der Leun, J.C., Kligman, L. and A.R. Young. UVA hazardsin skin associated with the use of tanning equipment. Photochem. Photobiol. B: Biol. 1989; 3:281-287.

Rundel, R. D., and D. S. Nachtwey. Skin cancer and ultraviolet radiation. Photochem. Photobiol.1 1978, 28:345-356.

Scotto, J., T. R. Fears, and J. Fraumeni. Solar radiation. In: **Cancer Epidemiology and Prevention,** Schottenfeld, D., Fraumeni, J. Eds., Saunders, 1982, 254-276.

Sober, A. J. Solar exposure in the etiology of cutaneous melanoma. Photo-Dermatol., 1987; 4:23-31.

Swerdlow, A.J., English, J. S., MacKie, R. M., O'Doherty, C. J., Hunter, J.A. and J. Clark. Fluorescent lights, ultraviolet lamps, and risk of cutaneous melanoma. Br. Med. J., 1988; 297:647-650.

Vázquez-Botet, M.,Torres, S.M., Sánchez, J.L. Malignant melanoma in Puerto Rico. Bol. Asoc. Med. P.R., 1983; 75:8-10.

Vázquez-Botet, M., Latoni, D., Sánchez, J.L. Malignant melanoma in Puerto Rico. Bol. Asoc. Med. P.R., 1990; 82:454-457.

Van der Leun, J. and F. R. de Gruijl. Influences of Ozone Depletion on Human and Animal Health. In: **UV-B Radiation and Ozone Depletion.** Effects on Humans, Animals, Plants, Microorganisms, and Materials, Tevini, M. Ed., Lewis Publishers, 1993, 95-123.

Vol. 90 • 1 - 2 - 3 / 1998 • Pág. 12, 15

Estudios Originales:

CCR5 chemokine receptor genotype frequencies among Puerto Rican HIV-1-seropositive individuals

Sandra Gonzalez, Grissell Tirado, Gonzalo Revuelta and Yasuhiro Yamamura[1]
Yuanan Lu, Vivek R. Nerurkar, Richard Yanagihara[2]

Key words: *CCR5, heterozygote, frequency, HIV-1, Puerto Rico*

Abstract: Some individuals remain uninfected by human immunodeficiency virus type 1 (HIV-1), despite multiple sexual contacts with subjects with confirmed HIV-1 infection. Several studies have confirmed that individuals who are homozygous for a 32 base pair (bp) deletion mutation in the chemokine receptor gene CCR5, designated as Δ32/Δ32, are protected against HIV-1 infection. Heterozygotes of the same chemokine receptor deletion mutation are, however, not protected from acquiring HIV-1 infection but seemingly have slower progression to acquired immunodeficiency syndromes (AIDS). Genotype frequencies of the Δ32 CCR5 mutation vary markedly among different ethnic groups; heterozygosity is found in approximately 15% of Caucasians, about 5-7% of Hispanics and African Americans and 1% or less of Asians. The ethnic background of Puerto Ricans is highly complex and usually includes admixture of Caucasian, Caribbean Indian and African traits to a varying extent. This study was conducted to examine the frequencies of the Δ32 CCR5 mutation among Puerto Ricans who are infected with HIV-1. Samples were received from different geographical regions of the island. Of 377 samples tested, 94.2% were wild type (non-deletion mutant) homozygotes, 5.8% were Δ32 CCR5 heterozygotes, and none were Δ32 CCR5 homozygotes. The incidence of CCR5 Δ32/w heterozygous mutation among Puerto Ricans seems to be somewhat lower than what was reported with US Hispanics. Some age and gender associated bias of the mutation frequency were observed with the study population, the reason for which is unclear at present.

Abbreviations

AIDS: Acquired immunodeficiency syndromes
HIV-1: Human immunodeficiency virus type 1
Δ32 CCR5: 32 base pair deletion mutation of CCR5 chemokine receptor gene
w/Δ32 and Δ32/Δ32: heterozygote and homozygote CCR5 deletion mutation

Introduction:

By 1996, the World Health Organization estimated that 22.6 million people were infected with HIV-1 (1). Although prevention methods are reducing the incidence of infection in some countries (2), the number of newly infected individuals is still increasing worldwide. There have been reports of individuals who have presumably been exposed repeatedly to HIV-1 but who have remained uninfected (3-6). CD4+ lymphocytes of these exposed but seronegative individuals have been found to be highly resistant to infection with HIV-1 strains which are primarily M-tropic but are still susceptible to T-tropic HIV-1 strains. Subsequent studies examining the possible effects of host genes on susceptibility to HIV-1 have confirmed the protective role of a Δ32 CCR5 mutation (3,5,7,8). For instance, Samson et al. (7) postulated that variants of CCR5 could be responsible for the relative or absolute resistance to HIV-1 infection exhibited by some individuals and also for the variability of disease progression in infected patients. They demostrated that a slow progressor and two seronegative controls exhibited heterozygosity at the CCR5 locus for a biallelic polymorphism. The mutant protein (Δ32 CCR5) lacks the last three transmembrane domains of CCR5, as well as the regions involved in protein coupling (7). In contrast to wild-type CCR5 (w/w), the trun-cated receptor (Δ32 CCR5) did not allow fusion with cells that were expressing HIV-1 env protein from either M-tropic or dual tropic viruses (7). Liu et al. (5) showed that two uninfected individuals that had multiple exposures to HIV-1 infection were homozygous for the defective allele (Δ32/Δ32). Population based studies have shown that Δ32/w (heterozygote) and Δ32/Δ32 (homozygote) CCR5 deletion genotypes are less frequent among non-Caucasian individuals. The Δ32/w CCR5 is found in approximately 13% of Native Americans, 6% of African Americans, 1% of Asians and 7% of Hispanics (2,8). Several other studies of non-Caucasians

[1] *Ponce School of Medicine AIDS Research Program, P. O. Box 7004, Ponce, PR 00732,*
[2] *Retrovirology Research Laboratory, Pacific Biomedical Research Center, University of Hawaii at Manoa, Honolulu, Hawaii 96816*
Address Correspondence to: *Yasuhiro Yamamura, Ph.D., Ponce School of Medicine, AIDS Research Program, P. O. Box 7004, Ponce, PR 00732, Telephone: (787) 841-5150/fax: (787) 841-5159, E-mail: yyl1 @coqui.net*

populations including HIV-l(+) and HIV-1(-) persons from Africa (3,7,8) Asia (3,7,8), Venezuela (2) and Haiti (3) have not found a Δ32/Δ32 (deletion homozygote) among these populations (2). Puerto Rico has the second highest incidence rate of AIDS in the United States territories. While Puerto Ricans are generally classified as "Hispanics" in the United States, genetic backgrounds of "Hispanics" are highly diverse. This study was initiated to evaluate whether the high rate of AIDS/HIV-1 infection in Puerto Rico was associated with the genetic makeup, and with the Δ32 CCR5 mutation rate in particular.

Methods:

Samples: Whole blood samples from HIV-1-positive individuals were obtained from various health care providers throughout Puerto Rico. For these samples, only minimal information was collected, such as age and sex to protect the confidentiality of the sample donors. No personal identifiers were used. Fresh samples were processed for DNA extraction as described below. Approximately 400 samples were chosen from more than 1,300 samples, and approximately equal numbers of samples were selected from each geographical region of Puerto Rico. The age and sex distribution of the study population is summarized in Table 1.

Table 1.
Age and gender bias of CCR5 deletion mutation among the Puerto Rican study population.

Groups	#with w/w CCR5	# with w/Δ32CCR5 (% frequency)
Age Groups (Years old)		
0-15	23	3 (11.5%)
16-30	45	4 (8.2%)
31-44	134	7 (5.0%)
>45	41	2 (4.7%)
unknown	112	6 (5.0%)
TOTAL	**355**	**22 (5.8%)**
Gender:		
male	219	18 (7.6%)
female	129	3 (2.3%)
unknown	7	1 (12.5%)

DNA extraction from whole blood samples: DNA was extracted from whole blood by a cell lysis process (9). Approximately 500 µl of lysis buffer (l0mM Tris-HCl, pH 8.3, plus 0.05% Triton) were mixed with 500 µl of whole blood. Samples were vortexed and centrifuged at 8,000 rpm for 1 minute. The supernatant was removed and the process repeated, using 1 ml of lysis buffer, until the supernatant became clear. Thereafter, the pellet was re-suspended in 1 ml of lysis buffer containing Proteinase K (10 mg / ml). DNA suspension was then incubated at 55°C for 1 hour and at 90°C for an additional 10 minutes.

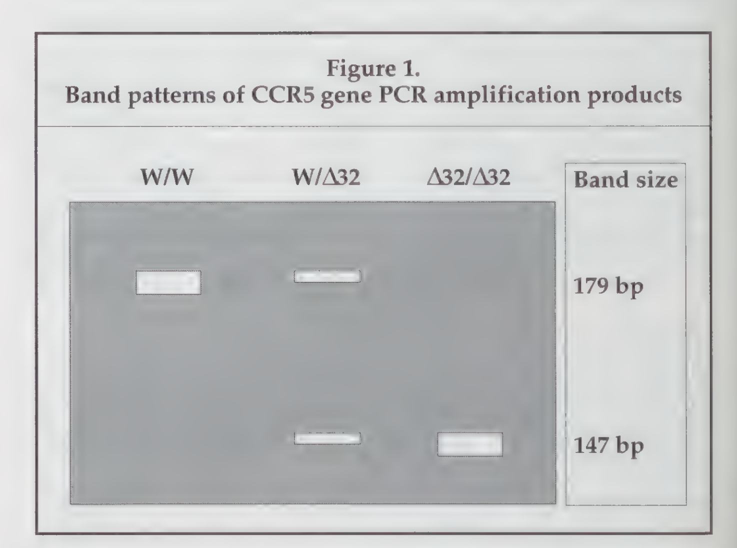
PCR amplification of CCR5 coding region: A selected region of the CCR5 gene spanning the portion of the deletion mutation, was amplified by polymerase chain reaction (PCR), using the primer pair,

5'-GTCTCTCCCAGGAATCATCTTTACCAGATCTC-3' (F/503/534), and
5'-TTAGGATTCCCGAGTAGCAGATGACCATGACA-3' (R/650-681)

Each 50 µ1 PCR mix contained 0.2-0.5 µg of DNA, PCR buffer (100 mM Tris-HCl, pH 8.3, 500 mM KCl), dNTP 200 IlM each, MgCl2 1.5 mM, primers 50 nM each, and 2.5 units of Taq-DNA polymerase. Amplification was performed by using a Perkin Elmer thermocycler model 9600 (Perkin Elmer, Norwalk, CT) as follows: first at 94°C for 5 minutes, followed by 45 cycles of 94°C for 1 minute, 60°C for 1 minute and 72°C for 1 minute; then a final extension at 72°C for 8 minutes and held at 4°C.

Polvacrylamide gel electrophoresis (PAGE) analysis of PCR product: PCR amplification products were analyzed by 10% PAGE. The expected PCR fragments were 179 bp for the homozygous wild type (w/w), 179 bp + 147 bp for the heterozygous (w/Δ32), and 147 bp for the homozygous deletion mutants (Δ32/Δ32). The band patterns for the CCR5 genotypes are shown in Figure 1.

Figure 1.
Band patterns of CCR5 gene PCR amplification products



DNA isolated from mononuclear cells were amplified for the CCR5 gene sequences, and the amplification products were identified by 10% PAGE, according to the methods described in the text. The figure shows, from right to left; molecular weight standard, 179 bp w/w CCR5 amplification product, and 179 and 147 bp w/Δ32 CCR5 amplification products. A negative control, a negative sample and four additional w/w CCR5 amplification products are also shown the figure.

Results:

Of the 377 DNA samples tested, 355 (94.2%) presented as wild type homozygotes (w/w), 22 (5.8%) were Δ32/w CCR5 heterozygotes, and none were Δ32/Δ32 CCR5 homozygotes. Table 1 shows frequency distribution of Δ32/w CCR5 heterozygotes by age group and gender. While the overall study population showed a heterozygote mutation frequency of 5.8%, the lower age groups tended to show higher genotype frequencies. For example, among those who were 15 years or younger, 3/26 (11.5%) were Δ32/w, while only 2/43 (4.7%) of those who were 45 years or older were Δ32/w. Eighteen of 237 males (7.6%) were Δ32/w, while only 3 of 132 (2.3%) females were Δ32/w heterozygotes.

Discussion:

Before the discovery of the role of specific host gene polymorphism in HIV- 1 infection, only HLA system genes were thought to protect against HIV- 1 infection (2). During 1996 and 1997, several studies have demonstrated the protective role of a 32 bp-deletion in the CCR5 chemokine receptor gene (Δ32 CCR5) against HIV-1 infection (3,5,7,8). This 32-bp-deletion, which causes a frame shift, was confirmed by sequencing several CCR5 PCR product clones (7). The frequent CCR5 allele corresponded to a previously published sequence (10). It had been demonstrated that CCR5 is the major co-receptor for primary M-tropic strains. Other chemokine receptors also known to serve as HIV-1 co-receptor are CCR2, CCR3, and CXCR4 (formerly LESTR) (7). CXCR4 is a major co-receptor for T-cell tropic HIV-l strains, and both CCR5 and CXCR4 serve as co-receptors for dual-tropic viruses (7). M-tropic HIV-1 strains predominate during the asymptomatic phase of the disease in infected individuals and are thought to be involved in HIV-1 transmission. Studies of resistance to HIV-l infection in exposed individuals have demonstrated that CCR5/Δ32 CCR5 can slow the progression to AIDS in seropositive patients (3). It has also been observed that homozygosity for the Δ32 CCR5 allele can account for resistance to HIV-l infection in some individuals (5,7). According to the expected Hardy Weinberg distribution, the genotype frequencies of the CCR5 and Δ32 CCR5 are anticipated to be 0.824 for w/w, 0.167 for w/Δ32, and 0.008 for Δ32/Δ32 CCR5 (7). The genotype frequencies observed in DNA samples from healthy individuals collected by the Genetics Department of the Erasme Hospital in Brussels were not significantly different from the expected. These data suggest that the null allele has no drastic effect on fitness. The consequences of this null allele in the normal Caucasian population were also considered in terms of susceptibility to HIV- l infection. In the same study, the CCR5 genotypes of 723 HIV-1-seropositive Caucasians were determined. A significant reduction in the frequency of the Δ32 CCR5 null allele was observed. This reduction was due to a decrease in the frequency of both w/Δ32 CCR5 heterozygote (0.108 versus 0.162) and Δ32 /Δ32 homozygote (0 versus 0.01). For both HIV-1(+) and HIV-1(-) population groups, only individuals from similar geographic origin and with European patronymic were included. These may imply that the observed differences in genotype frequencies are a consequence of a true difference in susceptibility to HIV- 1 infection rather than to different genetic backgrounds (7).

The values observed for CCR5 genotypes in the Puerto Rican seropositive population in this study differed from those found in one study for high-risk HIV-l(+) USA Caucasian (w/w = 77.4%, w/Δ32 = 22.6%, and Δ32/Δ32 = 0) and African American populations (w/w = 97.7%, w/Δ32 = 2.3%, and Δ32/Δ32 = 0), but are more similar to CCR5 genotype percentages found for a USA Hispanic population (w/w = 93.3%, w/Δ32 = 6.7%, and Δ32/Δ32 = 0) (8). The slight difference in frequencies for CCR5 genotypes between our present study with Puerto Rican and USA HIV-1(+) Hispanics could be a consequence of the genetic background of these two populations. The US Hispanic ethnic group includes Mexicans, South Americans, Puerto Ricans and other Latin American populations. Possible differences in genetic constituency among "Hispanics" may influence CCR5 deletion frequency as well as many other alleles. However, such a small difference could very well be due to the small sample size in this study. In the same US Hispanic study, HIV-1(-) blood donors showed a slightly lower w/Δ32 frequency of 6.9% and Δ32/Δ32 of 0.3%. The differences in CCR5 frequencies between HIV-1 (+) and HIV 1(-) Hispanics were almost identical with those previously described for HIV-1(+) and HIV-1(-) Caucasians (7). A population of HIV- 1(-) Puerto Ricans must obviously be included in future studies. The apparent differences observed in w/A32 frequencies among different age groups are interesting, as are the differences between the genders. At present, there are no data on whether the w/Δ32 mutation frequency is influenced by gender. Further studies with a larger sample size will show if the differences were real. A combined age and sex analysis would also provide additional information. These relationships have to be further investigated. Variants in another chemokine receptor, CCR2, have been described to have similar effects on HIV-1 infection to those described for the Δ32 CCR5 mutation (11). Studies of CCR2 genotype frequencies among the HIV- 1 (+) Puerto Ricans described in this study are currently in progress.

Acknowledgement:

This study was conducted as a part of activities by the Gateway Consortium formed by the AIDS

Research Programs at the University of Hawaii at Manoa (HI), New York City College of the City University of New York (NY) and Ponce School of Medicine (PR). This research was supported in part by NCRR-RCMI grant G12 RR 03050.

References:

1. World Health Organization: Acquired immunodeficency syndrome (AIDS) November 20, 1996. Wkly Epidemiol Rec 1996; 48:361

2. Mc Nicholl JM, Smith DK, Qari SH, Hodge T: Host genes and HIV: the role of chemokine receptor gene CCR5 and its allele (A32 CCR5). Emerg Infect Dis 1997; 3(3):261 -271

3. Fowke KR, Nagelkerke NJD, Kimani J, et al: Resistance to HIV-1 infection among persistently seronegative prostitutes in Nairobi, Kenya. Lancet 1996; 348: 1347-1351

4. Huang Y, Paxton WA, Wolinsky SM, et al: The role of mutant CCR5 allele in HIV - 1 transmission and disease progression. Nat Med 1996; 2: 1240-1243

5. Liu R, Paxton WA, Choe S, et al: Homozygous defect in HIV-1 co-receptor accounts for resistance of some multiply-exposed individuals to HIV-1 infection. Cell 1996; 86: 367, 377

6. Paxton WA, Martin SR, Tse D, et al: Relative resistance to HIV-1 infection of CD4 Iymphocytes from persons who remain uninfected despite multiple high-risk sexual exposures. Nat Med 1996; 2: 412-417

7. Samson M, Libert F, Doranz BJ, et al: Resistance to the HIV-l infection in Caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene. Nature 1996; 382: 722-725

8. Zimmerman PA, Bucklerwhite A, Alkhatib G, Spalding T, Kubofcik J, Combadiere C: Inherited resistance to HIV-l conferred by an inactivating mutation in CC chemokine receptor 5 — Studies in populations with contrasting clinical phenotypes, defined racial background, and quantified risk. Mol Med 1997; 3: 23-26

9. Higuchi R: Rapid efficient DNA extraction for PCR from cells or blood. Amplifications - A forum for PCR users (Perkin Elmer-Cetus) 1989; 2: 3

10. Samson M, Labbe O, Mollereau C, Vassart G, Parmentier M: Molecular cloning and functional expression of a new human CC-chemokine receptor gene. Biochemistry 1996; 35: 3362-3367

11. Smith MW, Dean M, Carrington M, et al: Contrasting genetic influence of CCR2 and CCR5 variants on HIV-1 infection and disease progression. Science 1997; 277: 959-9

- Nunca temas a las sombras. Solo constituyen el inicio de que en algún lugar cercano hay una luz resplandeciente.

Ruth Renkel

Vol. 90 • 1 - 2 - 3 / 1998 • Pág. 16, 20

Estudios Originales:

RT-PCR comparative study of viral load levels in the HIV positive population in Puerto Rico before and after protease inhibitor regimen implanted

Noemi Gonzalez, Nayra Rodríguez, Jose Tripari, Magda Cantisani, Nitza Moran[1]
Sylvette Soto, Carmen Feliciano, Pedro Ramos[2] and Yasuhiro Yamamural[1,3]

Key words: *HIV-1, Viral-load, Antiretrovirals, Protease-inhibitors, Puerto Rico*

Abstract: ***Ponce School of Medicine AIDS Research Program conducted a large scale viral load assessment of Puerto Ricans who are infected by human immunodeficiency virus type 1 (HIV-1) during the summer of 1996 through the Roche ACCESS program before general implementation of combination therapy. Since January 1997, it has monitored those HIV-1 patients who are under treatments at most HIV-1 health care clinics, including both public and private. The present study was conducted to evalute how the new treatment has generally impacted on the HIV-1 disease status of HIV-1 infected population in the eight Immunology Clinics. Assessment was made by consecutively monitoring the changes in HIV-1 viral load profiles of the population from January to September, 1997. A large majority of samples were delivered for viral load assessment without information of their treatment status, and only a small number of samples were identifiable either as baseline or followup. Despite the paucity of individual information, remarkable improvements of HIV-1 (+) population at large were evident. For example, in the summer of 1996 (ACCESS), population median viral load was 51,842; only 9% of the population had viral load less than 500 viral RNA copies/ml plasma and 72% had over 10,000 copies/ml. By July-September, 1997, the population median dropped to 8,679 (83%); 23% were below 500 copies/ml (+156%) and the proportion of patients who had over 10,000 copies/ml was reduced to 48% (-33%). The group of individuals who were positively identified as "follow-up" (i.e., under active treatment) had a median of 37128 copies/ml (-94%); 28 % were below 500 copies/ml (+211%) and only 40% had more than 10,000 copies/ml (-44%). It is obvious that the implementation of triple combination therapy by PASET in 1997, has very markedly improve the HIV-1 disease status of HIV-1 (+) population in Puerto Rico.***

Abbreviations used
HIV-1: Human immunodeficiency virus type 1

Introduction:

One of the substantial advances in the management of HIV infected persons has been the incorporation of protease inhibitors in the antiretroviral triple-drug regimen(1). Quantitation of HIV-RNA in plasma (viral load) is the standard tool used by health-care providers to determine when to start antiretroviral therapy and when to change current therapies. For example, a cohort analysis by Mellor et al.(2) clearly demonstrated that the viral load of patients was the single most direct predictor of AIDS development, and their survival time, etc. While viral load values of patients are quite closely associated with their peripheral CD4 T cell counts (3,4), viral load of a patient is much more closely associated with the progression of HIV- 1 associated diseases. Currently, initiation of therapy is recommended for all patientes with viral load levels greater than 5,000-10,000 copies/ml regardless of their peripheral CD4 T cell counts. Even those who still retain over 500 CD4 T cells/mm^3 blood may enter treatment, should their viral loads exceed 10,000 copies/ml. After FDA approval in July, 1996, of the Roche Amplicor HIV Monitor™ test, Ponce School of Medicine AIDS Research Program participated in a nationwide program, ACCESS, which provided free HIV-1 viral load testing for patients who had been under treatment. Over 1,300 patients in Puerto Rico received two baseline tests each. In January 1 997, the Puerto Rico Department of Health, through its 8 Immunology Clinics, began implementing new antiretroviral combination therapy which included HIV-1 protease inhibitors. Viral load assessments for patients under the new regimen were also performed by our program during January-

[1]Ponce School of Medicine AIDS Research Program, P. O. Box 7004, Ponce, PR 00732
[2]Puerto Rico Department of Health, PASET, Commonwealth of Puerto Rico
[3]Address Correspondence to: Yasuhiro Yamamura, Ph.D., Ponce School of Medicine AIDS Research Program P.O. Box 7004, Ponce, PR 00732, telephone: (787) 841-5150/ fax: (787) 841-5159 /e-mail: yyll @coqui.net

September, 1997, providing us the opportunity of evaluating the impacts of new antiretroviral combination treatment on HIV-1 infected cohort of Puerto Rico, in general. This report describes the results of first analysis which was conducted under an official agreement between the Puerto Rico Department of Health PASET (Programa Asuntos del SIDA y Enfermedades Transmisibles) and Ponce School of Medicine AIDS Research Program. Further detailed analyses are currently being organized to evaluate the efficacy of each different therapy regimen. Influence of past treatment history on therapeutic outcome of patients will also be critically evaluated.

Methods:

Test Samples:

Whole blood samples were collected at each participating Immunology Clinic, Puerto Rico Department of Health PASET, in EDTA tubes, and plasma separated immediately. Isolated plasma were either transported fresh within 6 hours (e.g., from Ponce Immunology Clinic) or kept frozen until transported to the laboratory according to the procedures mutually agreed on. Samples were given identification numbers by each clinic but no further personal identifier was used. Upon receiving, AIDS Research Program's laboratory assigned each sample a bar-coded number. Samples were identified in the laboratory's computer system only through bar-codes, except in offical reports to PASET which used laboratory numbers matched with respective PASET ID numbers.

Roche amplicor procedure:

Amplicor Monitor test is a combination of a reverse transcription-polymerase chain reaction (RT-PCR) process for HIV-1 sequence amplification and enzyme-linked probe-binding assay which is similar to enzyme linked immunosorbent assays (ELISA) commonly used. Assays were performed according to the manufacturer's protocol (5). Briefly, plasma was first mixed with lysis buffer to release free HIV-l viral RNA. The lysis buffer also contains an internal quantitation control which was used to compensate for recovery loss of the procedure. Then, viral RNA was precipated with alcohol, then diluted for PCR amplification. Amplicor HIV-1 Monitor procedure uses the amplification and detection of a 142 base pair, highly conserved region of the HIV- 1 gag gene. Amplification products were then chemically denatured and aliquots were added to separate wells of a microwell plate coated with HIV-I specific oligonucleotide probes. To achieve quantitative results over a large dynamic range, denatured samples were serially diluted in the microwell plate and after incubation, the amounts of specific HIV-I DNA bound to the probe were detected by an ELISA based method. Separate rows of serial dilution were also made to quantify internal quantitation (6). The optical density of reaction was measured at 450 nm and the adjusted quantity of viral RNA copies/ml was calculated according to the formula provided by the manufacturer's protocol.

Data storage & analysis:

The assay results were automatically transferrred to our NetServer using a custom-made program based on EXCEL. Stored data were analyzed by SPSS statistic software. Graphic presentations were made by using Microsoft Power Point software. The reference laboratory at Ponce School of Medicine mantains a data bank of all the viral load results done to our patients. The data was organized according to providers and to the following ranges: < 500 copies/ml, 500 -5000, 5001-10000, 10001-50000, 50001 100000, 100001 -200000, and > 200000 copies/ml using Microsoft Excel. The data is subsequently exported to SPSS statistical software for further analysis, that includes: the viral load range for the entire population during both periods described above, the mean, and the percentage of results in each of the ranges described above.

Results:

Changes in HIV Viral Load Profile of HIV-l (+) Population in Puerto Rico:

HIV viral load profiles, as assessed by Amplicor between the summer of 1996 and September, 1997, are summarized Figures 1-3. Even though the change was very slight in January-February, 1997 (Fig. 2), as compared to the pre-combination therapy phase (Fig. 1), very significant changes of the profile were evident by July-September (Fig. 3). Detailed information are provided in Table 1. For example, the viral load median of the population was 51,842 RNA copies/ml

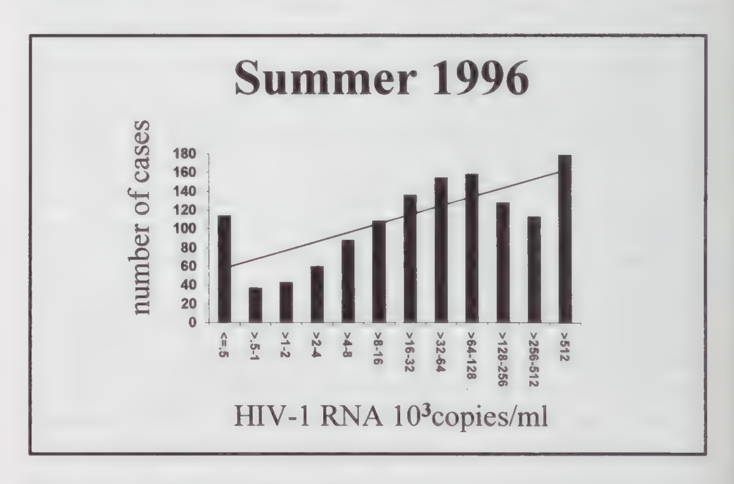


Figure l: *Distribution of HIV-l RNA viral loads obtained during summer 1996. A total of 486 viral load measurements were analyzed. Y-axis shows the number of cases and x-axis the copy number in log scale. The linear trend line was obtained by the least squares fit regression analysis which used the equation: y = mx + b where b is the intercept and m is the slope. Graphic was performed by an Excel based program Microsoft Power Point (version 7. O).*

in the summer of 1996. By January-February, 1997, when the entry screening for combination therapy was initiated, the median had dropped to 19,631. During April-May, 1997, a period when a majority of patients were still being screened, the median held steady at 21,969. However, in May-June, 1997, a significant decline of the population median was noted and further declined to 8,679 by July-September, 1997. Percentage of patients with 500 or less viral RNA copies/ml plasma proportionally increased from 9% in the summer of 1996 to 23% by July-September, 1997.

Simultaneously, the percentage of patients who had very high viral loads (e.g., over 200,000 copies/ml) declined from 25% to 13%.

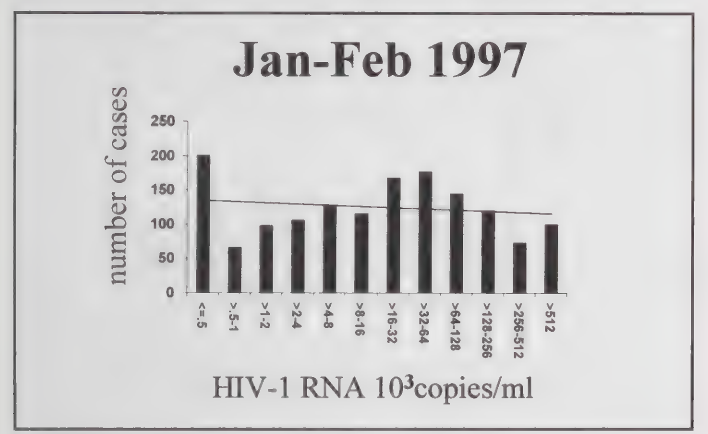


Figure 2: *Distribution of HIV-l RNA viral loads obtained during January-February 1997. A total of 1497 viral load measurements were analyzed. Y-axis shows the number of cases and x-axis the copy number in log_2 scale.*

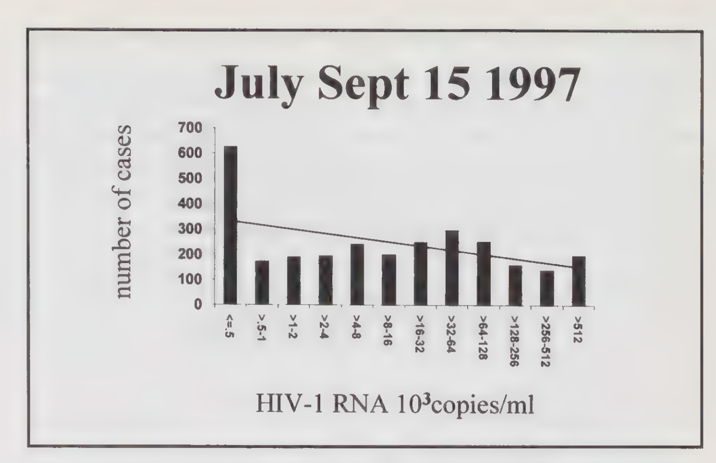


Figure 3: *Distribution of HIV-l RNA viral loads obtained during July-September 15, 1997. A total of 2,832 viral load measurements were analyzed. Y-axis shows the number of cases and x-axis the copy number in log_2 scale.*

Comparison between Baseline and Followup HIV Viral Load Profile of HIV- 1 (+) Population in Puerto Rico:

After the initial analysis, some samples were identified as baseline or as followup; their HIV viral load profiles are summarized in Figures 4 and 5, respectively. It is obvious that the follow-up group's viral load (Fig. 4) was very much reduced from that of the base line group (Fig. 5). For example, the viral load median of the baseline population was 10,493 copies/ml as compared 3,128 in the followup group. Percentage of patients with 500 or less viral RNA copies/ml plasma proportionally increased from 19 % in the baseline measurements to 28% in the followup data. Differences between the two groups were evident in each

Table 1.
Improvement of HIV status, following the '97 implementation of new triple combination protocols.

			Viral Load Ranges (% of total)						
Total # Tested	Range (min-max)	Median	<500	501-5000	5001-10000	10001-50000	50001-100000	100000-200000	>200,000
Pre-Therapy Population (Access: July-August, 1997)									
1,318	0-9.0 x 10^6	45,312	9%	12%	7%	24%	12%	11%	25%
Post-Therapy Population (1998)									
January-February									
1,497	0-7.5 x 10^6	19,631	13%	23%	7%	24%	11%	8%	14%
March - April									
2,203	0-6.4 x 10^6	21,969	13%	19%	9%	23%	11%	10%	15%
May - June									
2,105	0-6.3 x 10^6	14,651	17%	22%	8%	22%	10%	8%	13%
July - September									
2,923	0-6.5 x 10^6	8,831	23%	21%	8%	19%	10%	6%	13%

subcategory: e.g., 21% to 26% for 501-5,000 copies/ml grooup; 9% and 6% for 5,001-10,000 copies/ml; 20% and 18% for 10,001-50,000 copies/ml; 8% and 11% for 50,001-100,000; and 8% and 3% for 100,001-200,000 groups, respectively. Simultaneously, the percentage of patients who had very high viral loads (e.g., over 200,000 copies/ml) also declined from 15% to 8 %.

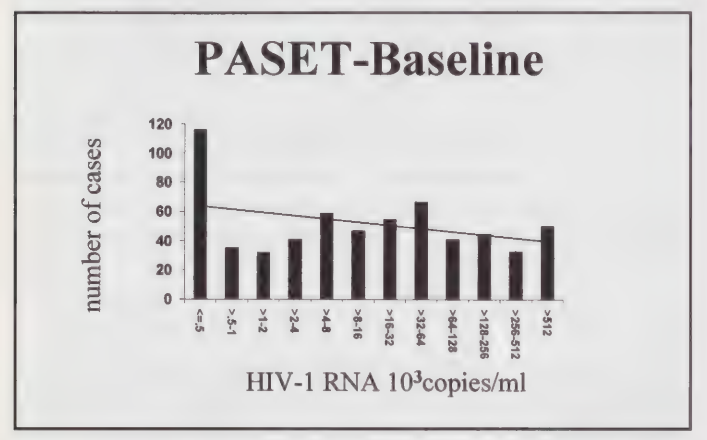


Figure 4: *Distribution of HIV-l RNA viral loads identified by the Department of H ealth as baseline measurements during the period of January- September 1997. A total of 621 viral load measurements were analyzed. Y-axis shows the number of cases and x axis the copy number in* log_2 *scale.*

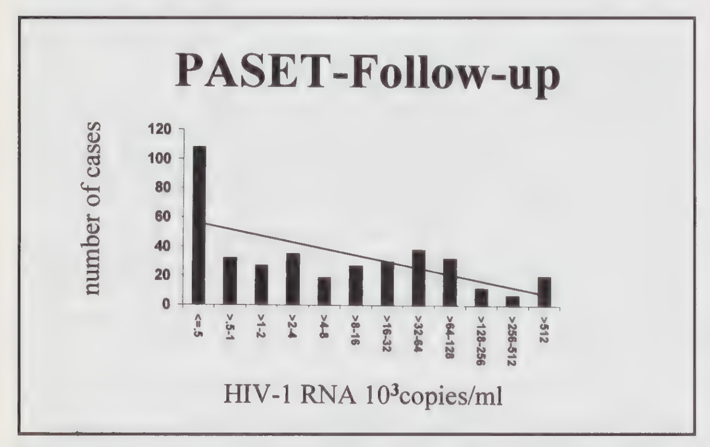


Figure 5: *Distribution of IIIV-I RNA viral loads identified by the Department of Health as follow-up measurements during the period of January- September 1997. A total of 387 viral load measurements were analyzed. Y-axis shows the number of cases and x-axis the copy number in* log_2 *scale.*

Comparison Between the HIV Viral Load Profile of HIV-1 (+) Patients in Several of the Immunology Clinics Participating in This Study:

Figure 6 represents the HIV viral load profiles (January-September, 1997), of patient population being treated at three representative immunology clinics, under PASET program of the Department of Health of Puerto Rico. There were significant differences in the viral load profile among the different clinics around the island. Patients in certain clinics seemed to have responded better to the therapy than those at others.

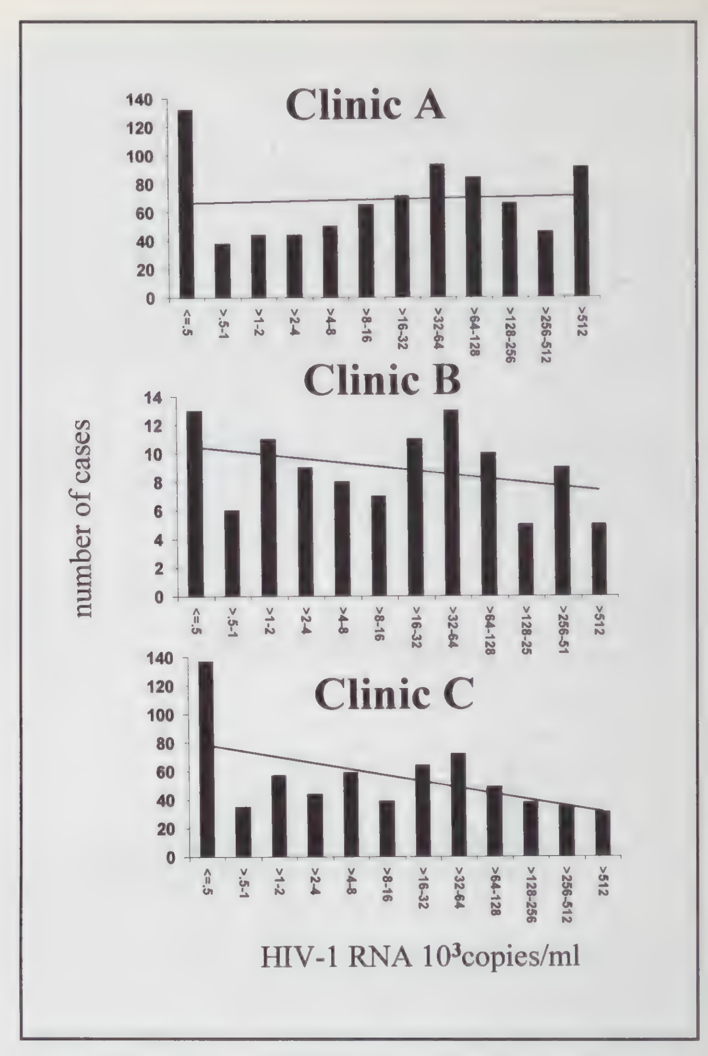


Figure 6: *Distribution of HIV-1 RNA viral loads obtained during the period of January-September 1997 among representative immunology clinics belonging to the Department of Health of Puertc Rico.Y-axis shows the number of cases and x-axis thecopy number in* log_2 *scale.*

Discussion and Conclusions:

HIV- 1 viral load assessment has been used not only to prognose but also to critically evaluate the efficacy of treatment protocols (7). The availability of data both prior to and during the implementation phase of the new combination therapy presented us with an unique opportunity to assess the efficacy of on-going as well as past antiretroviral treatment regimens in general HIV-l patient population. In the present analysis, we attempted to examine if the new therapy had significantly impacted on the disease status of the population. During the analysis, it was also noted that there seemingly are marked differences in the viral load profile of patient population, depending on at which clinics they were being treated.

First, we compared if the profile of the population had significantly improved between the time of ACCESS testing in the summer of 1996 and the initiation of screening for the new therapy in Janaury,

1997. The median viral load of population had declined from 51,842 viral RNA copies/ml in 1996 to 19,631 and 21, 969 in January February, and March-April, 1997, respectively, when most patients were being screened for the baseline values. Thus, it may be suggested that even prior to the implementation of new regimen including HIV- 1 protease inhibitors, antiretroviral treatment program of the Puerto Rico Department of Health PASET had significantly improved the disease status of Puerto Rican HIV- 1 (+) population in general. Alternatively, it may reflect the effort by PASET to recruit patients at earlier stages of the disease for the treatment program. During the May-June (1997) period, the viral load median of the population further declined to 13,173 RNA copies/ml, and by July-September (1997), during which time most of patients probably were in follow-up phases, the population median declined as low as 8,679 RNA copies/mk During a meeting in April (1997) between PASET and Ponce School of Medicine AIDS Research Program, it was agreed that subsequent samples would be identified either as baseline or as followup. Comparison of identified baseline samples and followup samples was more impressive. Namely, the baseline samples received during June-September, 1997, showed the median values of 10,493 copies/ml while the followup group had the median of 3,128. Nineteen percent of the former and 28% of the latter had viral load 500 copies/ml or less. While 23% or the baseline population had over 100,000 copies/ml only 1 1% of the latter showed the viral loads over 100,000 copies/ml. It is thus very evident that the new combination therapy being implemented by the Puerto Rico Department of Health PASET has been extremely successful and shown a great impact on slowing down and controlling the HIV-1 disease progression. It is, however, also to be noticed that even under the new program, a significant number of patients have failed to maximally respond. Possible influences of their past medication history need to be critically analyzed; which are the target of our on-going and future analysis.

On the other hand, there appear to be significant inter-institutional variations in the viral load profiles of patients under antiretroviral treatment programs of PASET. As shown by representative figures, efficacy of the treatments seem to differ very markedly from one clinic to the other. Reasons for this variability are unclear at present and may include multiple social as well as behavioral problems. For example, it is possible that patient population of a certain clinic may include higher proportion of non- or poorly compliant individuals, such as injecting drug users. It is also possible that the degree of compliance is affected by the quality of case-management being provided by the clinic. It is important to accurately assess the nature of compliance problems so that proper corrective measures may be instituted. It is also possible that patient enrollment progressed more rapidly in some clinical units than in others and the results may affect the viral load profile. For those individuals whose viral loads were reduced to below current detection level, i.e. < 400 copies/ml, there is a need for tests that are more sensitive and precise so we can monitor these patients better. For example, preliminary indications are that even among those with less than 400 copies/ml viral load, the virus tend to develop drug-resistance over time and eventually recur, unless the viral load is reduced to "virtual zero" (8). A new generation of "UltraSensitive" viral load assay (9), with a dynamic range of 50-50,000 copies/ml (Roche) is being made available. It is important that re-evaluation be implemented even for those individuals with less than 400 copies/ml viral loads, using the new more sensitive assay.

References:

1. Panel on Clinical Practices for Treatment of HIV Infection (Department of Health and Human Services and the Henry J. Kaiser Family Foundation): Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. November 5, 1997

2. Mellors JW, Rinaldo Jr CR, Gupta P, et al: Prognosis in HIV-l infection predicted by the quantity of virus in plasma. Science 1996; 272: 1167- 1170

3. Autran B, Carcelain G, Li TS, et al: Positive effects of combined antiretroviral therapy on CD4+ T cell homeostasis and function in advanced HIV disease. Science 1997; 277: 112-116

4. Carpenter CJ, Fischl MA, Hammer SM, et al: Anti-retroviral therapy for HIV infection in 1997: Updated recommendations ofthe International AIDS Society USA panel. J Am Med Assoc 1997; 277: 1962-1969

5. Quinn TM: Nucleic acid amplification assays for sexually transmitted disease: In: Lee, Morse, Olsvik. Eds. Nucleic acid amplification technologies, lt. Ed., Biotechniques Books, 1997, 219-223

6. AMPLICOR HIV-l MONITORTM test package insert, Roche Diagnostic System, Somerville, NJ (1996)

7. Saag MS, Holodniy M, Kuritzkes DR, et al: HIV viral load markers in clinical practice. Nat Med 1996; 2:625-629

8. Montaner JSG, Raboud JM, Rae S, et al. Full suppression of viral replication to below 20 copies/ml is needed to achieve a durable antiviral response. Abstract 105, Sixth European Conference on Clinical Aspects and Treatment of HIV Infection. Hamburg, Germany (October 1 1-15), 1997.

9. Mulder J, Resnick R, Saget B, et al: A rapid and simple method for extracting human immunodeficiency virus type 1 RNA from plasma: enhanced sensitivity. J Clin Microbiol 1997; 35: 1278-1280.

Estudios Originales:

Anti-fungal and cytokine producing activities of CD8 + T lymphocytes from HIV-1 infected individuals

María del Carmen Colón[1], Nilsa Toledo[2], Carlos León Valiente[3], Nayra Rodríguez[1], Noriko Yano[1], Herbert Mathews[4] and Yasuhiro Yamamura[1].

Key words:
LAK, IL-2 ACTIVATION, ANTIFUNGAL, LYMPHOCYTES, HIV-1 INFECTION, *Candida albicans.*

Abstract: Lymphokine activated killer (LAK) cells are capable of killing not only malignant cells but also hyphal form of Candida albicans in vitro. When peripheral blood mononuclear cells (PBMC) from normal healthy donors were cultured for 72-96 hrs with 1,500 international unit (IU)/ml interleukin-2 (IL-2), marked LAK activity was induced. However, even prior to IL-2 activation, PBMC isolated from some normal subjects and those from almost all individuals who are infected by human immunodeficiency virus type 1 (HIV-1) exhibited significant levels of anti-fungal activity. Such pre-activation ("in situ") antifungal activity of PBMC decreased during the initial 48 hrs of IL-2 activation. PBMC from HIV-1 seropositive subjects showed higher levels of "in situ" anti-fungal activity than normal PBMC did. After a decline of "in situ" activity during the initial 48 hours, LAK activity gradually increased and reached near maximal levels by day 4 and remained more or less constant until day 6. No significant difference was observed between the LAK activity of normal and HIV-1 (+) PBMCs on days 4-6. In IL-2 activated normal and HIV-1 (+) PBMC cultures, both CD4 and CD8 T cells produced IL-2, INF-γ as well as TNF-α. Production of IL-2 by both CD4 and CD8 T cells was suppressed in HIV-1 (+) PBMC cultures, but no significant suppression of INF-γ production was noted. Meanwhile, TNF-α production by CD4 was very much suppressed but no significant changes in TNF-α production by CD8 T cells was noted in HIV-1(+) PBMC cultures.

Abbreviations:
HIV-1: human immunodeficiency virus, type 1
IL-2: Interleukin-2
INF-γ: Interferon-gamma.
LAK: Lymphokine activated killer
PBMC: peripheral blood mononuclear cells
TNF-α: Tumor necrosis factor-alph

Introduction:

Candida albicans is a dimorphic fungus that is found in mammals as part of the normal microbial flora (Codish, et *al.*, 1976; Leherer, et al., 1978). This microorganism is a powerful biologic agent, capable of stimulating a variety of cell populations and of producing a range of immunologic effects (Diamond, et al. 1978; Diamond, et *al.*, 1981; Mahanty, et *al.*, 1988; Vecchiarelli, et al., 1989). The organism is an opportunistic pathogen which can produce life threatening diseases in mammalian host who are immunocompromised (Hurtrel, et *al.*, 1980; Baccarini, et *al.*, 1983; Cho, et *al.*, 1979). One of the most common immunosuppressive disease nowaday is the one caused by HIV-1; and C. *albicans* infection indeed is an extremely prevalent disease among HIV-1 seropositive subjects: most commonly oral, systemic or skin candidiasis (Silverman, et *al.*, 1990). The microorganism can induce the production of cytokines and the generation of effector cell populations that are cytotoxic for tumor cell targets in vitro (Cassone, et *al.*, 1987; Ausellio, et al., 1988). It also activates a lymphocyte population with an MHC unrestricted cytotoxic capacity, similar to that induced in lymphocytes by IL-2 (Ausellio, et al., 1989). The lymphokine -activated killer (LAK) cells have an MHC-unrestricted cytotoxicity and are activated in the presence of IL-2. This cells mediate the immunological response against tumor or malignant cells. This study reports the presence of unusual antifungal lymphocyte activity in some normal healthy subjects and in most of those with HIV-1 infection, as assessed as LAK activity against the hyphal form of *Candida albicans in vitro.*

Material and Methods

Blood Donors and Isolation of Peripheral Blood Mononuclear Cells (PBMC):
Venous blood samples were obtained from confirmed HIV-1 patients who were receiving treatments

[1]Ponce School of Medicine AIDS Research Program, P.O. Box 7004, Ponce, PR 00732;
[2]University of Puerto Rico, School of Dentistry, Oral Medicine Program, P. O. Box 36 5067, San Juan, PR 00936-5067.
[3]Bayamon Immunology Clinic, Hospital Universitario Ramón Luis Arnau, Calle Laurel, Urb. Santa Juanita, Bayamón, PR 00959.
[4]Loyola University of Chicago Stritch School of Medicine, Department of microbiology and Immunology, Maywood, Il 60153

for oral manifestation at the Oral HIV-1 Clinic at the Bayamon Immunology Clinic, Bayamon, PR. In total 55 patients participated in the present study, who were given full explanation of the study and voluntarily signed the study informed consent form. Both the study protocol and the informed consent form had been approved by the institutional review board (IRB) of the University of Puerto Rico Medical Sciences Campus, San Juan, PR. Their peripheral CD4 T cell counts ranged from 42 to 1,221/ul, with ages between 26 and 55 year old. Thirty four were males and 21 were females. Their clinical history including the past or current manifestation of oral candidiasis were also collected. Normal control samples were obtained from young, health donors who also signed informed consent form. Blood samples were collected at the clinic by venipuncture using Vacutainer tubes containing heparin (green-top) and forward immediately to the laboratory at Ponce School of Medicine AIDS Research Program, Ponce PR. Mononuclear cells were isolated by a Ficoll-Hypaque method and washed three times with RPMI-1640 medium before the assays.

Growth Inhibition of C. albicans:

Cultures of C. *albicans* were maintained at 25° C on Sabourand's dextrose agar (SDA) (Becton Dickin-son, Cockeysville, MD). For antifungal lymphocyte assays, fresh cultures were obtained by single colony isolation on SDA, which were cultured overnight at 37° C. Yeast form cells obtained from such cultures were suspended to 1 x 10^6 /ml in RPMI 1640 medium supplemented with 1 % Fetal Bovine Serum (Sigma Chemical Co., St. Louis), the assay medium, and 1 x 10^4 cells were placed in individuals wells of 96-well, flat bottom plates (Evergreen Scientific, Los Angeles, CA.). To obtained hyphal form, the plates were incubated at 37°C in 5% CO_2 for 2 hrs. Peripheral blood mononuclear cells (PBMC) were isolated, as described above, and were placed in each well at the PBMC to fungi ratios of 25:1 to 6:1. The cultures were incubated at 37°C in 5% CO_2 for additional 3 hrs. and PBMC were lysed and removed by washing with water. Then, 0.2 ml of RPMI 1640 containing 2μCi of [^{3}H]- Uridine (Amersham Life Science, Arlington Heights, IL) was added to each well. Following 1 hr. incubation at 37° C 5% CO_2, 50 μl HBSS containing 25 U Lyticase (Sigma Chemicals, St. Louis, MO) was added to individuals wells for 0.5 hrs at 25°C. Cells were harvested with PHD cells harvester and radioactivity of each sample was assessed by a beta counter. Growth inhibition of C. *albicans* was calculated as

% inhibition = {[(dpm C. *alhicans* Control) - (dpm effector and C. *albicans* - effector control) / dpm C. *albican.s* Control]} x 100.

IL-2 Activation of PBMC:

PBMC were suspended at 2.5 x 10^5/ml in RPMI-1640 plus 10% FCS, supplemented withl,500 U/ml IL-2, and one ml suspension was incubated in a 5 ml volume Falcon tube (Becton Dickinson) for 5 days. For a time-course study, cultures were harvested after incubation of 0, 1, 2, 3, 4 and 5 days by centrifugation, and the cells were washed three times with RPMI 1640 medium with 10% FCS. Cell concentration was determined by direct counting in hemocytometers and was adjusted accordingly for antifungal assay. Recombinant IL-2 preparation was kindly provided by the National Cancer Institute, National Institutes of Health (Bethesda, MD).

Production of Cytokine:

PBMC were suspended at 1 x 10^6 /ml in the culture medium supplemented with 1,500U/ml IL-2, and at various time of incubation, cells were collected and washed with RPMI 1640. Cells were then stimulated for 10 hours with the combination of anti-CD3 murine monoclonal antibody (IgE), murine anti-CD28 antibody (both from Research Diagnostics, Flanders, NJ) and phorbol 12-myristate acetate (PMA) (Sigma) at 37° C. Monensin (20μM) (Sigma) was added to the stimulated cultures for the last 6 hrs. of culturing to prevent trans membrane secretion of intracellularly produced cytokines. Monensin treatment allows accumulation of cytokines at higher intracytoplasmic concentrations so that they can be detected by flow cytometry. The cells were wash twice with staining buffer (Dulbeco's PBS, 1% FCS and 0.1% Sodium azide, pH 7.4-7.6) and fixed with 0.5% paraformaldehyde (PFA) and stored at 4°C overnight. The cells were then harvested by centrifugation and were resuspended in 4% PFA for 30 min at 4°C. After 30 min incubation, the cells were washed with staining buffer and treated with 50 μl of permeabilization buffer (Dulbecco's PBS, 1% FCS, 0.1% sodium azide, 0.1% saponin, PH 7.4 -7.6). Anti-cytokine monoclonal antibodies conjugated with phycoerythrin (PE) (FL-2) were added to cell pellet and incubated for 30 min at 4°C. The cells were wash twice with permeabilization buffer and treated simultaneously with anti-CD3 fluoresceine isothiocyanate (FITC) (FL-1) conjugate and anti-CD8 Per-CP (FL-3) conjugate for 30 minutes. Cells were then washed and finally suspended in 600 μl of staining buffer for analysis by flow cytometry.

Data acquisition and analysis:

FACScan® (Becton Dickinson) equipped with a Power-Macintosh 7600® computer with Consort 32® software was used for data acquisition. Lymphocyte gate was first drawn by using forward and side scatter channels and T lymphocytes were identified by logical gating of CD3 (FL-1) positive "lymphogate" events. CD8 positive and negative T subsets were the further "logically" gated and were analyzed for each cytokine producing (FL-2 positive) and non producing (FL-2 negative) subpopulations, respectively. In this study, CD8 (FL-3) negative T cells were arbitrarily classified

as CD4 T cells but may include some other T cell subsets which are CD3 positive but negative for both CD4 and CD8 markers.

Results:

Cytokine Profile of PBMC's from HIV-1(+) and HIV-1(-) donors:

Representative cytokine profiles of PBMC, prior to IL-2 activation, from HIV-1 (+) and HIV-1 (-) individuals are shown in Figure 1. While IL-2 production by CD4 T cells became somewhat depressed in HIV-1 (+) PBMC, production of the same cytokine by CD8 T cells very markedly increased in HIV-1 (+) PBMC. A very similar trend was observed for tumor-necrosis factor-alpha (TNF-α). No significant amount of IL-4 was produced by either normal CD4 or CD8 T cells but a significant amount of the cytokine was produced HIV-1 (+) CD8 T cells accompanied by much lesser production by HIV(+) CD4 T cells. Most marked changes were noted with interferon-gamma (IFN-γ), which was produced almost exclusively by CD4 T cells in normal PBMC cultures but was produced only by CD8 T cells in HIV-1 (+) PBMC cultures. IL 2 activation of normal PBMC generally increased production of all cytokines except IL-4. Increases were more notable with CD8 subset of T cells, though no significant reduction of cytokine production by CD4 T cells was evident. IL-2 activation of HIV(+) PBMC, on the other hand, significantly increased production of all cytokines by CD4 T cell subset, but simultaneously the production by CD4 T cells was markedly suppressed (Figure 2).

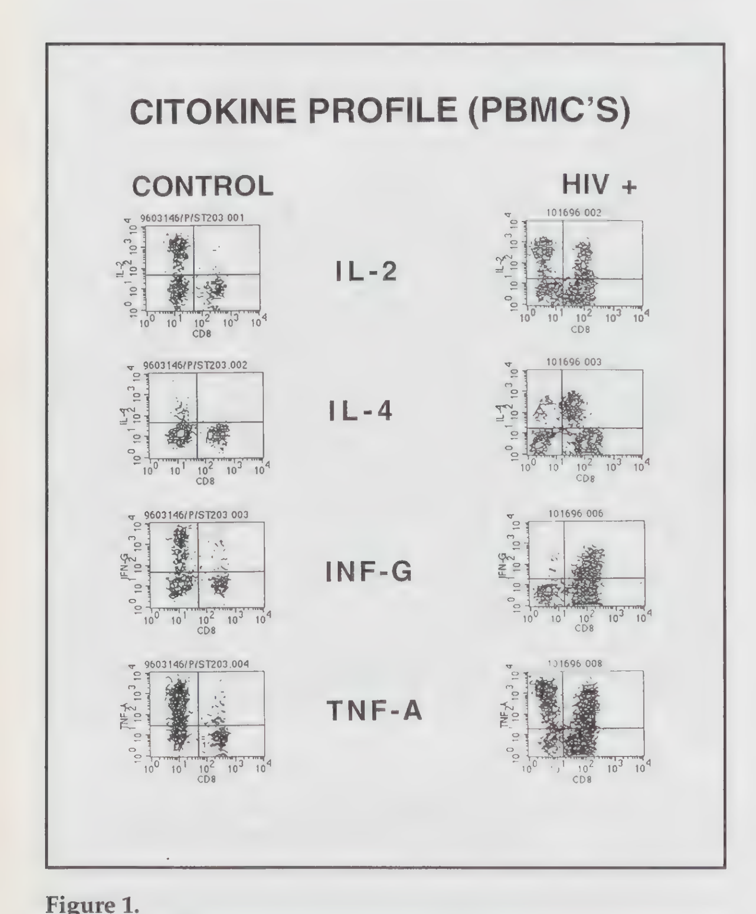


Figure 1.
Cytokine production by pre-activation PBMC from normal control and HIV-1(+) individuals. Cells were stimulated by combination of anti-CD3, anti-CD28 monoclonal antibodies plus PMA, as described in the text, and processed for detection by flow cytometry. The figures show representative profiles of a control (leit column) and an HIV-1 (+) individual (right). Cytokine producing cells (y-axis positive) were analyzed for both CD8 (x-axis positive) and CD4 (x-axis negative) T cell subsets, respectively. Profiles are shown for IL-2, IL-4, IFN-y and TNF-a, from the top to the bottom.

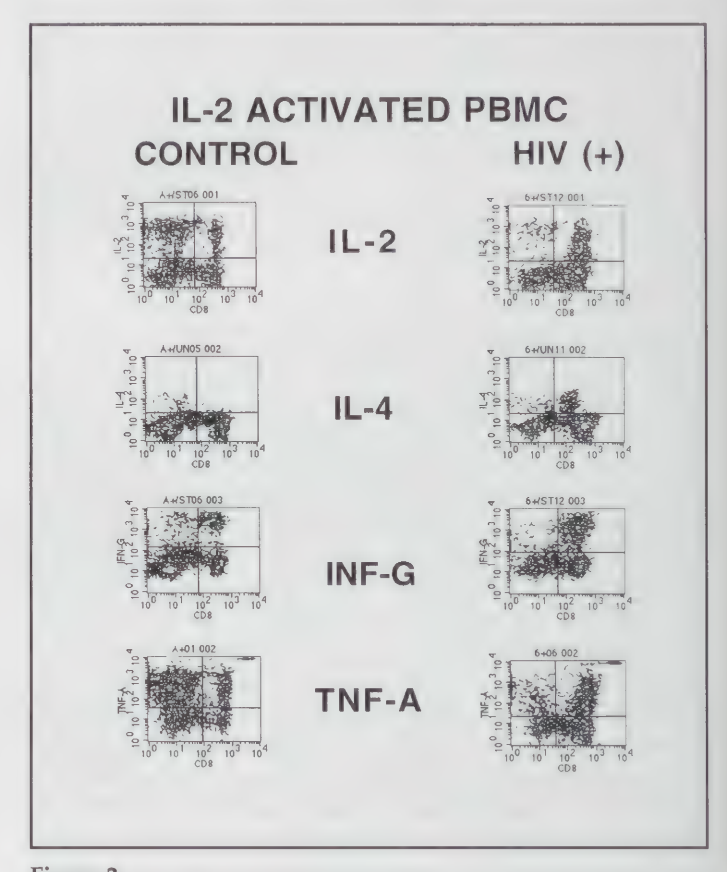


Figure 2.
Cytokine production by IL-2 activated PBMC from normal control and HIV-1(+) individuals. PBMC were cultured with 1,500 IlJ/ml IL-2 for six days and then were activated and processed as described in Figure 1 legend.

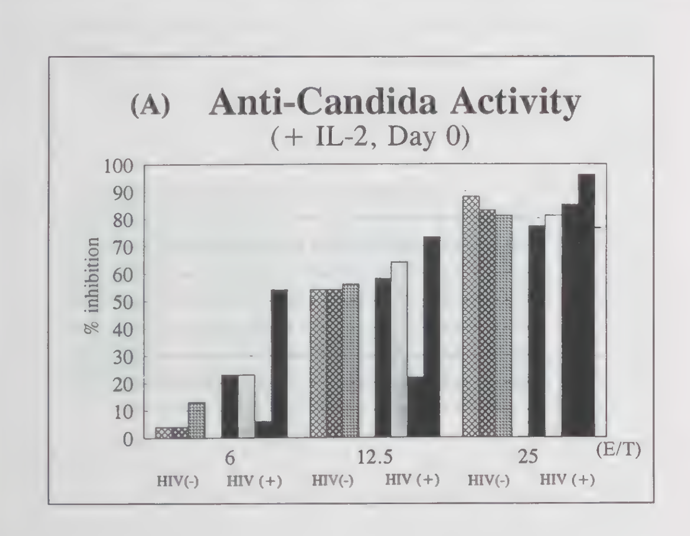
IL- 2 Induction of Antifungal Activity:

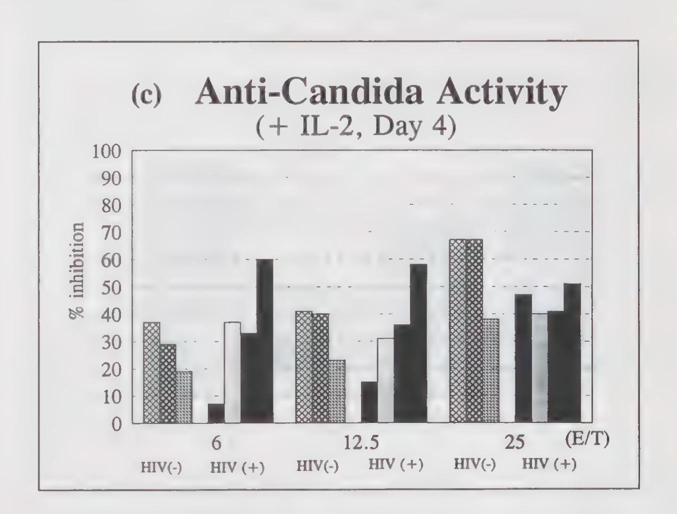
PBMC were activated with IL-2 and samples were taken at different time of culturing up to 6 days and the lymphocyte antifungal activity was assessed, as described above. As shown in Figures 3a-d, antifungal activity of most (if not all) PBMC cultures including those form normal as well as from HIV-1 (+), significantly declined by day 2, but thereafter steadily regained up to day 6. *In situ* antifungal activity was significantly lower with PBMC from normal HIV-1(-) individuals as compared to HIV-1 (+) PBMC (Fig. 3a). But LAK activity, which could be typically assessed

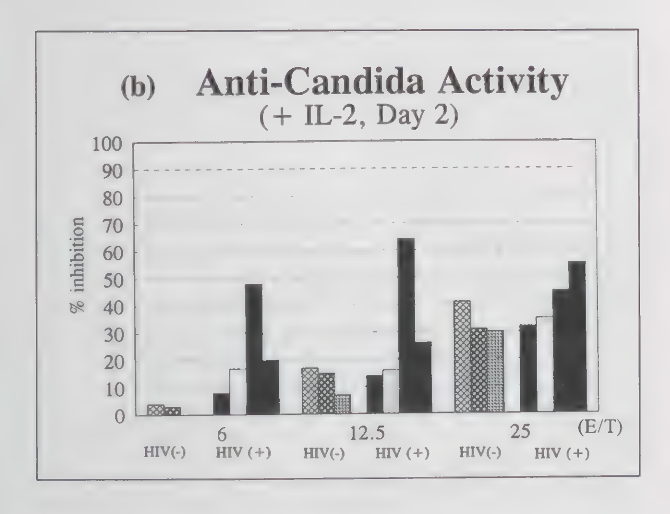
on day 6, did not seem significantly different between HIV-l(-) and HIV-1(+) (Fig. 3d). Etfector dose response curve of *"in situ"* antifungal activity (Fig. 3a) was quite different from that of LAK (Fig. 3d), also suggesting that the modes of two antifungal activities are also distinct from each other.

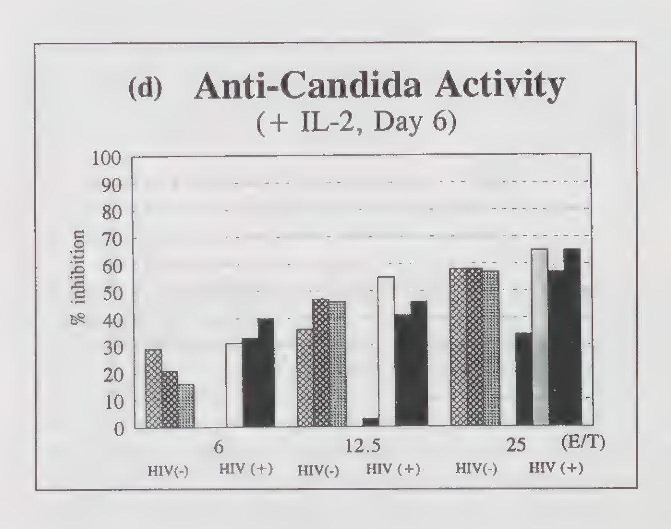
HIV-1 Disease Status and Cytokine Producing Ability of T cells:

It was also examined if the disease status of HIV-1(+) individuals, as expressed by their peripheral CD4 T cell counts, is directly associated with cytokine producing ability of their T cell subsets. Figures 4 and 5 summarize the IL-2 and IFN-γ producing ability (% positive cells) of T cells as related to their peripheral CD4 T cell count status, respectively. The percentage of IL-2 producing CD4 T cells progressively declined from about 42% in normal to, 38%, 23% and 7% in those HIV-l(+) with >500, 200-499, and <200 CD4 T cells, respectively (Fig. 4a). The cytokine was produced by 42% of normal CD8 T cells, and by 42%, 31 %, and 18% of CD8 T cells from HIV-1(+) individuals with >500, 200-499, and <200 CD4 T cells. Decline ofthe cytokine production was much more gradual with CD8 than CD4 T cells (Fig. 4b). Interferon gamma production by either T cell subset, however, was virtually unaffected by the disease status of HIV-l (+) individuals. Approximately 14-20% of CD4 T cells and 27-30% of CD8 T cells produced the cytokine regardless of their HIV- 1 disease status (Figure 5a-b).









Figures 3a, -b. -c & -d.
In vitro anti-fungal activity of PBMC pre- and post-IL-2 activation. PMBC from either normal health HIV-I(-) donors or irom confirmed HIV-1(+) individuals were cultured with 1,500 IU/ml IL-2, as described in the text. Cells were harvested at various time aiter addition of IL-2, washed and their antiiungal activity against hyphal form of Candida albicans, as described in the text. Antiiungal activity was expressed as % inhibition of the control cultures. Antifungal activity of activated PBMC were assayed at the effector/target ratio of 25: 1, 12.5: 1, and 6: 1, respectively. Assays were periormed 011 day-0 (immediately after IL-2 addition) (3a), day 2 (3b), day4(3c)andday6(3d).

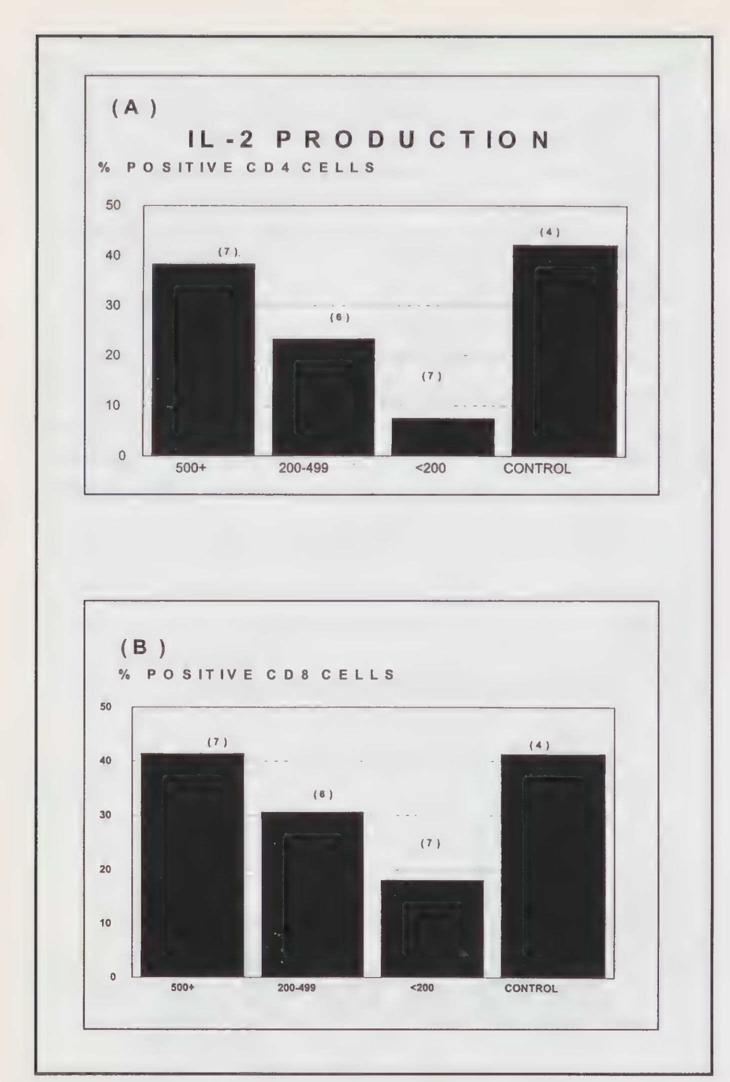


Figure 4.
IL-2 production by T cell subsets of normal donors and of HIV- I (+) individuals at different disease status. PBMC were activated as described above, and were analyzed by flow cytometry for IL-2 production for both CD4 (A) and CD8 (B) T cell subsets. HIV-1(+) individuals were grouped by their peripheral CD4 T cell counts. Cytokine producing ability was expressed as percent cytokine positive cells for each subset. Disease status is arbitrarily defined by the peripheral CD4 T cell counts of individual patient (x-axis).

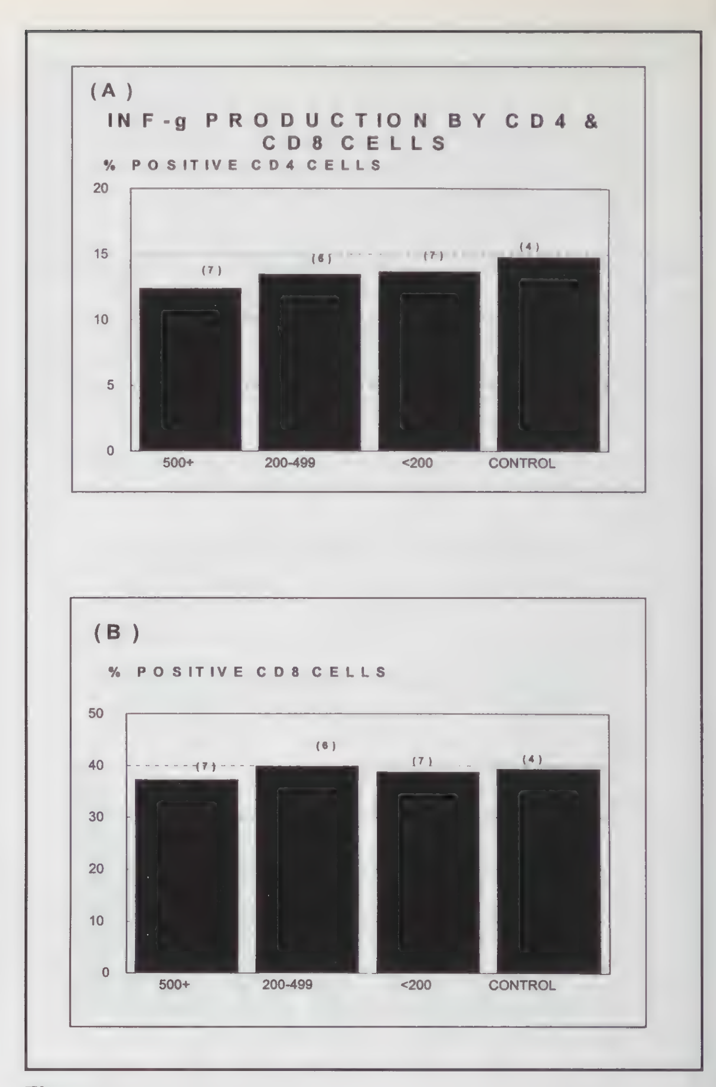


Figure 5.
IFN-y production by T cell subsets of normal donors and of HIV-1 (+) individuals at different disease status. PBMC were activated as described above, and were analyzed by flow cytometry for IFN-y production for both CD4 (A) and CD8 (B) T cell subsets. HIV-1(+) individuals were grouped by their peripheral CD4 T cell counts. Cytokine producing ability was expressed as percent cytokine positive cells for each subset. Disease status of patients are defined by their peripheral CD4 T cell counts (x-axis).

Discussion

Previously, David and his colleagues (1995) demonstrated that IL-2 activated Iymphocytes, LAK, killed *in vitro* not only malignant cells but also hyphal form of *Candida albicans.* We thus hypothesized that frequent development of oral or esophageal candidiasis in HIV- 1 infected individuals may be associated with changes of their antifungal LAK cell activity. It was, therefore, rather unexpected that some PBMC either from HIV-l(-) or HIV-l(+) subjects also exhibited strong antifungal activity against C. *albicans.* However, this *"in situ"* antifungal cytotoxicity was reproducibly observed with numbers of normal healthy as well as HIV- 1 (+) individuals, with probable exceptions of those with very advanced HIV- 1 (+) disease. The *"in situ"* cytotoxicity, however, significantly declined by day 2, after which time IL-2 activated LAK activity began to increase. LAK activity reached maximal levels by day 4-5 and remained rather stable till day 7 or 8 (data not shown). Dose response curves of *"in situ"* and LAK antifungal effector lymphocytes were quite different from each other, suggesting that these activities probably were mediated by two different types of cells. Nature of *"in situ"* cytotoxic lymphocytes is unknown at this time. Part of such activity may very well be associated with a population(s) of cytotoxic T lymphocytes which are specifically primed with C. *albicans* antigens through natural exposure. Indeed, most healthy individuals are antigenically primed by his ubiquitous microorganism and the microbial antigen is often used as a "recall antigen" to assess the immunocompetence of HIV-l(+) individuals. Possible correlation of *"in situ"* antifungal

activity levels with the patients' skin reactivity to the antigen may need to be evaluated. We are currently also investigating if the past or current manifestation of candidiasis actually influenced the levels of antifungal activity. The results of the study will be described elsewhere.

The pattern of modified cytokine production by HIV-1 (+) individuals' T lymphocytes was predicted by our previous study (Rodriguez, N., et al. 1997.), even though the finding does not fit the classic T_H1 -T_H2 functional switch of T cells suggested as the basis of HIV-1 mediated immunodeficiency (Caruso, A., et al. 1995; Clerici, M., et al ,1993a; Clerici, M., et al., 1993b; Clerici, M., et al, 1992; Haraguchi, S., et al., 1995.). Namely, HIV-1 infection was described to be closely associated with a progressive decline of IL-2 production by CD4 T cells. Our present study, on the one hand, supports those observations. However, our present study also showed that IL-2 production by the other T cell subset, CD8, declined much more slowly. On the other hand, the production of another T_H1 cytokine, IFN-γ was not significantly altered. Indeed, there seems to be even a slight increase of the cytokine production as HIV-1 disease progressed. However, the viral infection actually caused a drastic shift of the cytokine producers, from CD4 T cells to CD8 T cells. Production of (presumably) the same cytokine but by a different cell type may signal a significant alteration of biological processes. However, the nature of such biological alteration, should it have actually occurred, is yet unknown to us at present. It should also be noted that the cell population which we arbitrarily termed as "CD4" T cells may include some other minor CD4-CD8-T cell subsets such as most of those with or/and some of those with oc/13 T cell receptor subtypes. Cytokine producing proper-ties and alteration of the properties in HIV-I infected individual are not well understood for these minor, more defined subpopulations. Additional analysis are obviously needed to further define the properties of T cell subsets which are possibly affected by the viral infection.

Possible link between the change of T cell immune function, as measured by their cytokine production profile, and either "in situ" or LAK antifungal lymphocyte activity could not yet be found through the present study. Possible influence of co-existing clinical conditions of patients on either cytokine production or/and antifungal lymphocyte activity still need to be explored. However, our present approach and methodology may help others with similar interest to further address these questions.

Acknowledge

The present study was supported in part by NCRR-RCMI grant G12RR03050. Support by staff of Bayamon Immunology Clinic are also very deeply acknowledged.

References

Ausiello, C., A. Maleci, G. C. Spagnoli, G. Antonelli, and A. Cassone. 1988. Cell mediated cytotoxicity in glioma-bearing patients. Differential responses of peripheral blood mononuclear cells stimulation with interleukin-2 and microbial antigen. J. Neuro-oncol. 6:329.

Ausiello, C. M., C. Palma, G. C. Spagnoli, A. Piazza, C. U. Cascciani, and A. Cassone. 1989. Cytotoxic effectors in human peripheral blood mononuclear cells induced by a mannoprotein complex of *Candida albicans* a comparison with interleukin-2 activated killer cells. Cell Immunol. 121 :349.

Baccarini, M., F. Bistoni, P. Puccetti, and E. Garaci. 1983. Natural cell-mediated cytotoxicity against Candida albicans induce by cyclophosphamide: nature of the in vitro cytotoxicity effector. Immun. 42:I.

Beno, D. W. A., A. G., Stover, and H. L. Mathews. 1995. Growth inhibition of *Candida albicans* hyphae by CD8+ lymphocytes. J. Immunol. 5273: 5281.

Beno, D. W. A., and H.L. Mathews. 1993. Quantitative measurement of lymphocyte mediated growth inhibition of *Candida albicans*. J. Immunol. Methods 164: 155.

Cassone, A., P. Marconi, and F. Bistoni. 1987. Cell well of *Candida albicans* and host response. Crit. Rev. Microl. 15:87.

Codish, S.D., and S. Tobias. 1976. Managing systemic mycoses in the compromised host. JAMA 235:2132.

Cho, Y. S., and H. Y. Choi. 1979. Opportunist fungal infection among cancer patients. A ten year autopsy study. Am. J. Clin. Pathol. 72:617.

Diamond, R. D., and C. C. Haudenschild. 1981. Monocyte-mediated serum-independent damage to hyphal and pseudo-hyphal forms of *Candida albicans* in vitro. J. Clin. Invest. 67: 173.

Diamond, R. D. , and R. Krzesicki. 1978. Mechanisms of attachment of neutrophils to *Candida albicans* pseudohyphae in the absence of serum, and of subsequent damage to pseudo-hyphae by microbicidal processes of neutrophils in vitro. J. Clin. Invest. 61 :360.

Hurtrel, B., P. H. Lagrange, and J. C. Michel. 1980. Systemic candidiasis in mice. II. Main role of polymorphonuclear leuko-cytes in resistance to infection. Ann. Immunol. C 131: 105.

Leherer, R.I., E. R. Stiehm, T. J. Fisher, and L. S. Young. 1978. Severe Candida infections. Clinical perspective, immune defense mechanisms and current concepts in therapy. Ann. Intern. Med. 89:91

Mahanty, S., R. A. Greenfield, W. A. Joyce, and P. W. Kincade. 1988. Inoculation candidiasis in murine model of severe combined immunodeficiency syndrome. Infect. Immun. 56:3162.

Silverman, S. Jr., L. Laungjarmekorn, J. Gallo, and C. Migliorati. 1990. Findings and management in 50 HIV-infected patients with positive oral cultures. Int. Conf. AIDS. 6 (2):394.

Vecchiarelli, A., E. Cenci, M. Puliti, E. Blasi, P. Puccetti, A. Cassone, and F. Bistoni. 1989. Protective immunity induce by low-virulence *Candida albicans* cytokine production in the development of the anti-infectious state. Cell Immunol. 124:334.

Vol. 90 • 1 - 2 - 3 / 1998 • Pág. 27, 29

Artículos de Repaso:

Fear Research: Implications for Anxiety Disorders

Gregory J. Quirk, Ph.D.
Assistant Professor - Dept. of Physiology,
Ponce School of Medicine, Ponce, P.R.

In recent years, emotion has gained newfound respectability as a subject of study by neuroscientists. The 27th Annual Meeting of the Society for Neuroscience, last October, featured an unprecedented number of sessions and lectures in the area of emotion. This resurgence is due to recent successes in the study of one emotion in particular: fear. Fear is easy to elicit in experimental animals, and the behavioral and physiological correlates of fear are also easily measured. Thus, the tools of modern neuroscience can be used to unravel the mysteries of this particular emotion in experimental animals. In humans, the recent advances in brain imaging techniques has allowed fear processes to begin to be visualized in people.

One hopeful promise of fear research is to explain the neural basis of anxiety disorders, such as phobias and post-traumatic stress disorder (PTSD). It has been hypothesized that deficits in the fear learning system may underlie these anxiety disorders, and a more thorough knowledge of the fear learning system will lead to more effective treatments.

Fear Conditioning

A useful tool for studying fear learning is classical (Pavlovian) fear conditioning. In this paradigm, a neutral conditioned stimulus (e.g. a tone) is paired with an aversive unconditioned stimulus (e.g. a shock). After only a few such pairings, the heretofore neutral stimulus comes to elicit a range of species-specific fear responses in the subject. These include autonomic changes such as increased blood pressure, hormonal changes, and behavioral changes such as "freezing". These responses allow the animal to evade detection or escape a potential predator. Fear conditioning is observed in many species, and is thought to be evolutionarily conserved[1]. Such fear responses occur automatically in response to natural threats (i.e. a cat, for a rat). Fear conditioning enables the animal to apply automatic danger-avoidance systems to new stimuli, thereby increasing its chances of survival in an unpredictable world.

Fear memories resulting from traumatic experiences can leave lasting scars. PTSD, which is most often observed in combat veterans but has also been observed in victims of political violence[2], results in persistent flashbacks, panic attacks and autonomic changes when the sufferer is re-exposed to stimuli associated with the original traumatic event. It has been proposed that fear conditioning could account for such associative responses[3,4].

Extinction of Fear

Once fear conditioning is acquired, repeated presentation of the conditioned stimulus in the absence of the unconditioned stimulus leads to diminution of fear responses, a process known as extinction. Like acquisition, the extinction of inappropriate fear responses is also behaviorally adaptive. Does extinction erase the fear memories acquired during fear conditioning? The evidence suggests not. Pavlov himself noted that, after completely extinguishing the conditioned response in his dogs, the mere passage of time would cause "spontaneous recovery" of the responses[5]. More recent data shows that changing the experimental context (chamber) or giving unsignalled shocks to the extinguished animal can reinstate conditioned responses[6]. Thus, fear memories appear to be indelible[7] and extinction causes inhibition of the response to the fear-inducing stimulus, without erasing the underlying fearful memory. A failure of neural mechanisms underlying extinction could explain the persistence of traumatic memories in PTSD or phobias that are resistant to treatment[3]. The reinstatement phenomenon bears close resemblance to the reactivation of stress disorders that can occur many years after a traumatic event[8]. For example, the death of a parent or loss of a job can cause dormant anxieties to re-awaken. Important research questions include: where are the permanent fear memories stored? Which structures are responsible for inhibition of fear responses during extinction, and later reactivation of such responses?

Correspondence: Gregory J. Quirk, Ph.D.
Dept. of Physiology Ponce School of Medicine
P.O. Box 7004, Ponce P.R. 00732-7004 • Tel. 787-844-1980 • Fax: 787-841-1040 - email: greg@cns.nyu.edu

The Amygdala

The central brain structure in fear conditioning is the amygdala, a subcortical nucleus situated in the temporal lobe. Damage to the amygdala in laboratory animals[9,10] and humans[11,12] prevents fear conditioning without interfering with unconditioned autonomic arousal. Much of what we know about the pathways of fear conditioning comes from the work of LeDoux and coworkers (see ref. 9 for a review). They have shown that the amygdala receives auditory and somatosensory input directly from the thalamus, and projects to the hypothalamic and midbrain areas that mediate the autonomic and behavioral fear responses (see fig. 1). Thus, the amygdala can mediate fear conditioning without cortical involvement, although cortical areas may modulate fear responses via projections to the amygdala. For example, lesions of sensory cortex and prefrontal cortex have no effect on acquisition of fear conditioning, but block extinction. This suggests a possible role of these structures in inhibiting fear responses during extinction.

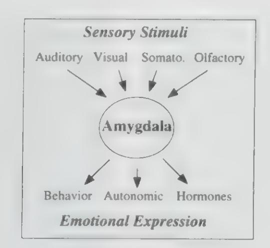


Figure 1.
Sensory stimuli from all modalities are received by the amygdala, which detects danger and initiates emotional responses via descending projections to hypothalamic and brainstem sites. (Adapted from ref. 14).

Neuronal Activity in Fearful Animals

While lesion studies have told us much about the role of the amygdala and related structures in fear conditioning, the technique is limited because it is difficult to infer normal function from a damaged brain. Recent advances in electrode technology and software development have made it possible to monitor the activity of multiple, simultaneously recorded neurons in the amygdala of awake animals undergoing fear conditioning (fig. 2). With this technique the response of neurons to auditory stimuli can be measured, as well as the correlation of each neuron's activity with other neurons. The post-stimulus time histogram (figure 3a) shows the number of times a cell fired when the tone was presented. Cross-correlograms (fig. 3b) show the occurrence of spikes of one cell, with respect to the occurrence of spikes of a second cell. If two cells tend to fire at the

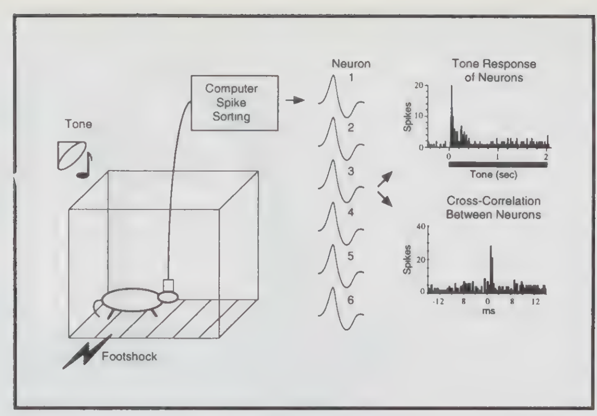


Figure 2.
In fear conditioning, the rat is exposed to paired tones and footshocks and acquires a defensive "freezing" response to the tone. Multi-wire extracellular electrodes record action potentials from multiple amygdala neurons. Once digitized, the action potentials from each neuron are sorted by specially designed software, and graphed relative to the occurrence of the tone (post-stimulus time histogram, upper), or relative to the occurrence of action potentials from other neurons (cross-correlogram, lower).

same time, a peak is observed at 0 ms in the cross-correlogram. In the amygdala, fear conditioning increased both the tone responses and cross-correlation of neuronal activity[13]. This suggests that conditioning can potentiate sensory inputs to the amygdala, as well as modify the strength of connections between cells in the amygdala. Conditioning-induced changes in amygdala tone responses occurred at the shortest possible latency following tone onset (12 ms), suggesting potentiation of direct thalamic input, rather than less direct cortical inputs[14]. Extinction training reversed the tone response changes but left some conditioning-induced correlational changes intact (fig. 3). This suggests that while sensory inputs to the amygdala are reset by extinction, some trace of the fear experience in the amygdala persists throughout extinction.

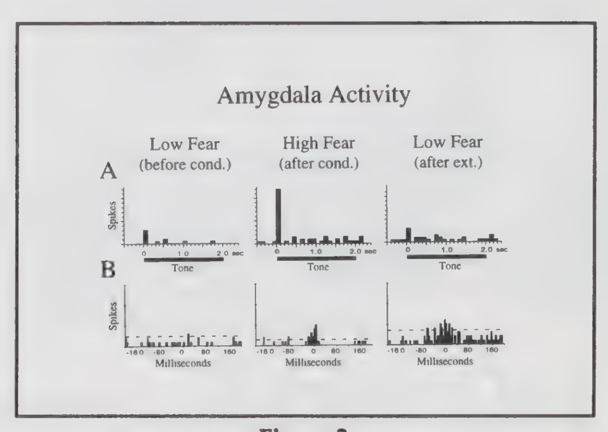
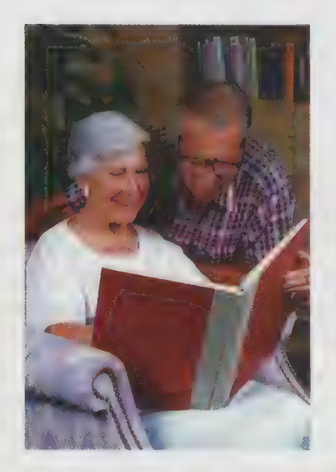


Figure 3.
A. Fear conditioning increases the tone responses of amygdala neurons, especially at the onset of the tone (compare "before conditioning" to "after conditioning"). These changes are reversed after extinction trials (adapted from reference 16).
B. Conditioning also increases the correlation between neurons, but these changes persist throughout extinction trials, leaving a trace of the experience in the amygdala (adapted from reference 13).



Contribuyendo a mejorar la calidad de los servicios de salud







Nuestra Misión...

Mejorar la calidad del cuidado de la salud del pueblo de Puerto Rico a través de la investigación, evaluación, educación, y la diseminación de información a los proveedores de salud y los consumidores.



Similar to the amygdala, neurons in the auditory cortex increase their tone responses during fear conditioning. However, unlike the amygdala, increases in cortical tone responses persist throughout extinction trials[15]. This suggests that the auditory cortex may be a storage site of some aspect of fear conditioning, and is not subject to inhibition during extinction trials. In animals without an amygdala, auditory cortex cells retain their ability to condition, but lose their persistence during extinction trials[16]. This suggests that the amygdala facilitates long-term storage of fear memories in cortex, and that cortex could play a key role in the inhibition of responses during extinction.

Future Directions

In order to elucidate the functional circuits of fear and anxiety, future work will focus on the interactions between the amygdala and cortical areas during acquisition and extinction of fear conditioning. Improved behavioral measures of fear (more sensitive than freezing) must be closely compared to unit responses in cortico-amygdala circuits. Recording simultaneously from small groups of neurons will show how fear learning alters the synaptic connections within "cell assemblies" and reorganizes functional circuits. In addition to sensory cortex, the association cortical areas are particularly important. A recent brain imaging study showed enhanced activity in the prefrontal cortex and amygdala in PTSD patients who had been reminded of their traumatic experience[17]. The hippocampus is critical for associating a shock with the environmental context in which the shock occurred[18]. Functional connections between the amygdala and hippocampus are just starting to be explored.

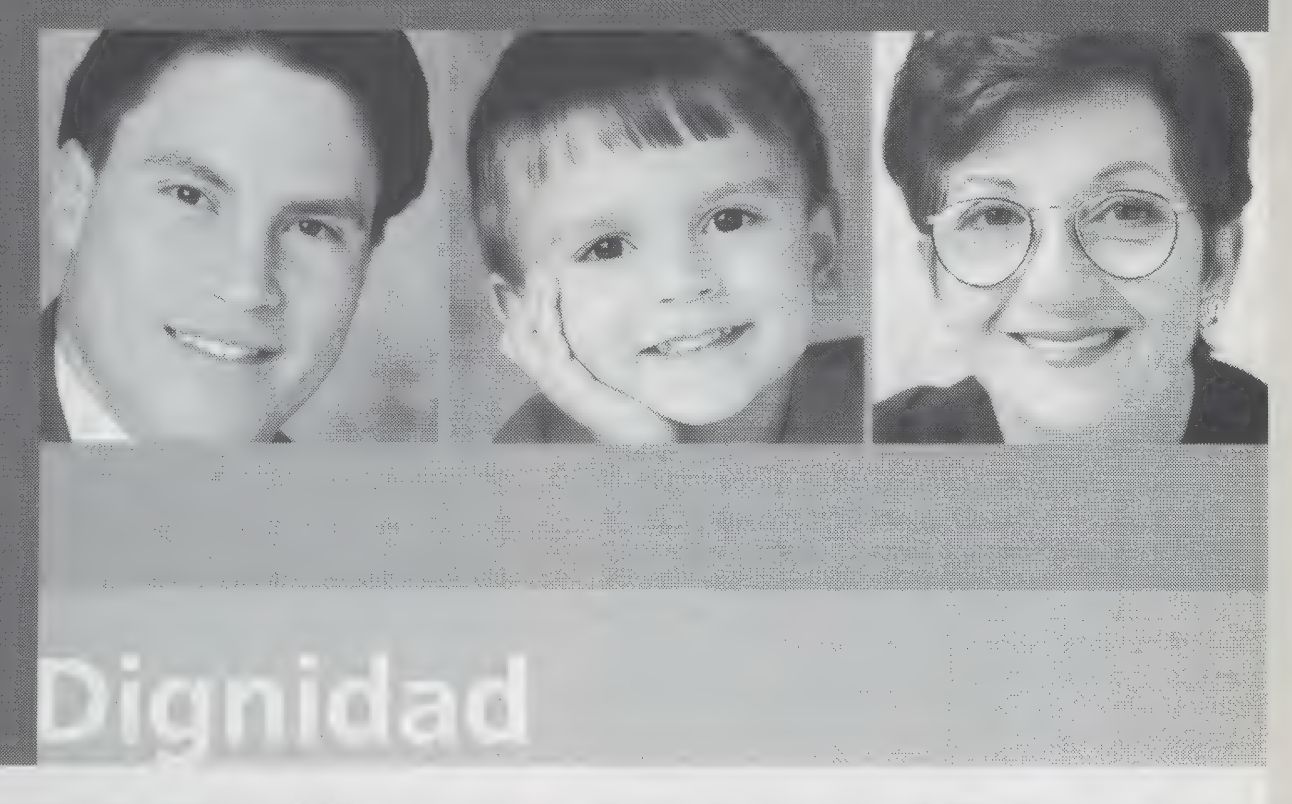
What clinical gains can be expected from this basic research? One can imagine that as the fear circuit is better understood, pharmacological and behavioral interventions will be more specific and effective. For example, it has been envisioned that future drugs may act specifically on the sensory inputs to the amygdala to decrease modality-specific fear in patients[3], and new behavioral therapies will recall the context of extinction in order to prevent relapse in PTSD sufferers[6]. In the process, we will learn more about our emotional machinery, which plays such a key role in guiding our behavior.

References

1. Ohman A. Fear and anxiety as emotional pheno-mena: clinical, phenomenological, evolutionary perspectives, and information processing mechanisms. In Handbook of the Emotions, M Lewis and J M Haviland, eds (New York: Guilford), 1992; 511-536.
2. Quirk GJ, Casco L. Stress disorders of families of the disappeared: a controlled study in Honduras. Soc Sci Med 1994; *39*:1675-1679.
3. Charney DS, Deutch AY, Southwick SM, Krystal JH. Neural circuits and mechanisms of post-traumatic stress disorder. In Clinical Consequences of Stress: From Normal Adaption to PTSD, MJ Friedman, DS Charney, AY Deutch, eds (Phila-delphia, Lippincott-Raven), 1995; 271-287.
4. Shalev AY, Rogel-Fuchs Y, Pitman RK. Conditioned fear and psychosocial trauma. Biol Psych 1992; *31*:863-865.
5. Pavlov IP. Conditioned Reflexes. London: Oxford University Press, 1927.
6. Bouton ME. Context, ambiguity and classical conditioning. Cur Dir Psychol Sci 1994; *3*:49-53.
7. LeDoux JE, Romanski LM, Xagoraris A. Indelibility of subcortical emotional memories. J Cog Neurosci 1989; *1*:238-243.
8. Solomon Z, Garb R, Bleich A, Grupper D. Reactivation of combat-related posttraumatic stress disorder. Am J Psychiatry 1987; *144*:51-55.
9. LeDoux JE. Emotion: clues from the brain. Ann Rev Psychol 1995; *46*:209-235.
10. Davis M. The role of the amygdala in emotional learning. Int Rev Neurobio 1994; *36*:225-266.
11. LaBar KS, LeDoux JE, Spencer DD, Phelps EA. Impaired fear conditioning following unilateral temporal lobectomy in humans. J Neurosci 1995; *15*:6846-6855.
12. Bechara A, Tranel D, Damasio H, Adolphs R, Rockland C, Damasio AR. Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. Science 1995; *269*:1115-1118.
13. Quirk GJ, Repa JC, LeDoux JE. Fear conditioning enhances short-latency auditory responses of lateral amygdala neurons: parallel recordings in the freely behaving rat. Neuron 1995; *15*:1029-1039.
14. Quirk GJ, Armony JL, Repa JC, Li XF, LeDoux JE. Emotional memory: a search for sites of plasticity. In Cold Spring Harbor Symposium on Quantitative Biology, Vol 61, B Stillman, ed (New York: Cold Spring Harbor Press), 1996; 247-257.
15. Quirk GJ, Armony JL, LeDoux JE. Fear conditioning enhances different temporal components of tone-evoked spike trains in auditory cortex and lateral amygdala. Neuron 1997; *19*:613-624.
16. Armony JL, Quirk GJ, LeDoux JE. Differential effects of amygdala lesions on early and late plastic components of auditory cortex spike trains during fear conditioning. J Neurosci 1998; *18*:2592-2601.
17. Rausch SL, van der Kolk BA, Fisler RE, Alpert NM, Orr SP, Savage CR, Fischman AJ, Jenike MA, Pitman RK. A symptom provocation study of posttraumatic stress disorder using positron emission tomography and script-driven imagery. Arch Gen Psychiatry 1996; *53*:380-387.
18. Phillips RG, LeDoux JE. Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. Behav Neurosci 1992; 106:274-285.

Todos los seres humanos nacen libres e iguales en dignidad y derechos.

Declaración Universal de Derechos Humanos (1948) Artículo 1



Es la manera como toda persona merece ser tratada. Y en ella se basa la filosofía Humana, la compañía líder* de planes de salud en Estados Unidos, ahora en Puerto Rico.

En Humana ofrecemos a nuestros clientes el servicio que queremos para un familiar. Porque reconocemos que las personas tienen derecho a recibir el cuidado correcto, en el momento correcto, y en el lugar correcto.

Estamos a tu orden las **24 horas**, **365 días** al año. Llámanos al **282-7900**, libre de cargos al **1-800-314-3121** o a tu agente de seguros.

Porque todos merecemos servicios de salud de calidad, con dignidad.



http://www.humana.com.

Humana Health Plans of Puerto Rico, Inc. • Humana Insurance of Puerto Rico, Inc.
Este anuncio ha sido sometido para la aprobación del Comisionado de Seguros de Puerto Rico el 13-3-98.
*IAC Newsletter Database Faulkner and Gray, Inc. Medicine and Health January 12, 1998.

Artículos de Repaso:

Caveolae a new subcellular transport organelle

Silva1 W, Maldonado H.[1], Chompré G, and Mayol N .[1]

Key Words: *endothelial cells; caveolae; caveolin; signal transduction*

Abstract: ***Recent advances have allowed the identification and characterization of well defined vesicular subcellular organelles involved in multiple basic cellular physiological processes, with demonstrated clinical relevance. Among these, three particular subcellular organelles have received special attention based on their proven and postulated participation in the sorting and targeting of small-and large -molecular weight molecules during exocytosis and endocystosis, and in cell signaling and transduction events. These have characteristic proteinaceous coat structures that allows their classification accordingly, into what has been described as clathrin coated vesicles, COP-coated vesicles and caveolae. In this review article a brief description of clathrin-coated vesicles and COP-coated vesicles is presented. Caveolae (CAV), in turn, constitute a novel subcellular organelle that has received special attention based on its proven and postulated participation in transcytosis, potocytosis, and in cell signaling and transduction events. In this review of the literature a more extensive discussion is presented of CAV. In this context the article discusses the structural features of caveolae, its constituent protein caveolin(s), the functional aspects of this new organelle, and its postulated clinical relevance.***

Introduction

Recent advances have allowed the identification and characterization of well-defined vesicular subcellular organelles involved in multiple basic and essential cellular physiological processes, with demonstrated pathophysiological and clinical relevance. Among these, three vesicular subcellular transport organelles have received special attention based on their proven and postulated participation in the sorting and targeting of small- and large- molecular weight molecules during exocytosis and endocytosis, and in cell signaling and transduction events. These organelles are vesicular structures that share the basic property of processing a surrounding well-defined and distinctive coat structure. The specific components of the coat structure have allowed their classification and nomenclature based on the principal protein constituents. These coated vesicular organelles are thus called clathrin-coated vesicles (CCV), COP coated vesicles and caveolae. In this review article we describe some basic aspects of CCV and COP-coated vesicles, and further emphasize on the emerging knowledge of caveolae (CAV).

Clathrin coated vesicles. Probably the most characterized of these are (CCV). In 1961, Gray described for the first time some specialized vesicles in synaptic terminals of cerebellar neurons, which he called "complex vesicles". Similar vesicles were also described in early morphological studies of other tissues and cells, and described then as "bristle-coated", "alveolate", "densely-rimmed", and "coated vesicles" (See Nevorotin, 1980). After the landmark work by Pearse (1976) on the biochemical isolation and purification of the main polypeptide component of these coats, clathrin (180 kDa), the term clathrin-coated vesicles (CCV) was coined for this class of vesicles. Today we know that all these descriptive names allude to the characteristic icosahedral protein cage or coat surrounding the vesicles made up of clathrin (Pearse1 1976), the clathrin light chains (CLC (Kirchhausen and Harrison1981; Ungewickel and Branton, 1981; Lisanti et al., 1982; Brodsky et al., 1990), and the assembly polypeptide (AP) complexes or adaptors (Pearse, 1978; Woodward and Roth, 1978; Schook et al., 1979; Keen et al.,1979; Unanue et al., 1981; Pearse1 1982).

Functionally CCV are now know to participate in the sorting of lysosomal enzymes (Campbell and Rome, 1983; Campbell et al., 1983) and in the regulated secretory pathway of peptides in the trans Golgi network (TGN) (Orci et al., 1984; Tooze and Tooze, 1986; Orci et al., 1987). In the plasmalemma, CCV are involved in receptor mediated endocytosis (RME), transcytosis diacytosis, and recycling of specific molecules (Heuser and Reese, 1973; Broun et al., 1980). Specific subpopulations of CCV involved in the above cellular processes correlate with the differential expression of specific adaptors (AP1, AP2 and AP3).

Department of Pharmacology & Toxicology, Ponce School of Medicine, Ponce P R., and Department of Pharmacology, Universidad Central del Caribe, Bayamón, P R.
Address Correspondence to: *Dr. Walter 1. Silva, Department of Pharmacology and Toxicology, Box 7004, Ponce School of Medicine, Ponce, Puerto Rico 00732-7004. Tel/Fax: 787-841-1040 e-mail address: WIS0123@aol.com*

COP-coated vesicles. Since the pioneer studies on CCV, other non-clathrin coated vesicular organelles have been described with an emerging role in vesicular transport and membrane trafficking. Among these we have the novel non-clathrin coated vesicles involved in the bulk flow of constitutive secretory and membrane proteins along the *cis* to *trans* Golgi axis (Rothman and Orci, 1992).

A characteristic coat structure denominated the coatamer has been identified, which is also composed of various polypeptides with remarkably similar molecular weights as those of the CCV, referred to as the COP proteins. Indeed, one of these, beta-COP, has been shown to bear a great degree of homology to the beta-adaptins of the AP complexes of CCV (Serafini et al., 1991). This group of vesicles can be referred to as COP-coated vesicles. Heterogenecity of COP coated vesicles has also been determined and recent studies establish the existence of COP I and COP ll vesicle subpopulation involved in the anterograde and retrograde vesicular transport between the rough endoplasmic reticulum and the *cis* Golgi compartment.

Caveolae, structural aspects. Approximately forty years ago, specialized 50-100 nm diameter invaginations associated with the plasma membrane of many cell types were described and identified (Palade, 1953; Palade and Bruns, 1968). Today, the list of cell types where CAV have been identified include smooth muscle cells, cardiac muscle, epithelia, endothelial cells, astrocytes and adipocytes. Structural studies indicate that caveolae are decorated on their cytoplasmic surface by a unique array of filaments or strands that form striated coatings. The coat cannot be removed by washing with high salt however, exposure of membranes to cholesterol-binding drugs, such as filipin and nystatin, leads to a dissapearance of these striated cytoplasmic coat-structures of the plasmalemma and their invaginations (Lisanti et al., 1995; Anderson, 1993).

Caveolae are flask-shaped non-clathrin-coated invaginations of the plasma membrane. These structures seem to define micropatches or microdomains in the plasma membrane. Current methods for purifying caveolae from tissue culture cells take advantage of the Triton x-100 insolubility of this membrane domain. A detergent-free method for purifying caveolae membrane from cultured cells has recently been developed that enables us to identify caveolae associated proteins that had previously gone undetected (Smart et al., 1995). These studies have identified caveolin, a 21kDa membrane protein, originally described as a primary vSRC tyrosine kinase substrate, as a principal constituent of CAV (Glenney and Soppet, 1992; Rothberg et al., 1992; Kurzchalia el al., 1994). Caveolin has the capacity of forming oligomeric structures of higher molecular mass, and at least two isoforms (alpha and beta, 24 kDa and 21 k Da, respectively) are known to be expressed (Lisanti et al., 1993). The expression of these isoforms seems to be dependent on the availability of two distinct translational initiation sites at met 1 and met 32, leading to two isoforms that consequently primarily differ in their N-terminal sequences (Scherer et al., 1995). More recently additional caveolin variants have been identified and cloned, these have been referred to as caveolin-2 and caveolin-3 (Tang et al., 1996). The functional relevance of these isoforms is an active area of research.

Of major relevance to the biogenesis of caveolae, Smart et al., (1996) from Dr. R. Anderson's laboratory have demonstrated that the caveolae's cyclic transition from a flat segment of membrane to a vesicle that then returns to the cell surface is hormonally regulated. This cycle seems to depend on a population of protein kinase C-alpha (PKC-alpha) molecules that reside in the caveolae membrane where they phosphorylate a 90KDa protein, a requirement for caveolae internalization. Conditions that inhibit this phosphorylation and treatment with histamine inhibit the invagination step. Histamine's effect was blocked by pyrilamine but not cimetidine, indicating the involvement of histamine H1 receptors. All togethers, these findings suggest that the caveolae internalization cycle is hormonally regulated.

Caveolae, functional aspects. Plasmalemmal caveolae were first identified as an endocytic compartment in endothelial cells, where they appear to move molecules across the cell by transcytosis. CAV have also been found to be enriched in GPI-anchored proteins (Lisanti et al., 1995), thus evidencing their role in cell polarity and sorting. This biochemical segregation of membrane constituents is accompanied by a corresponding specialization of functions, such as transcytosis, potocytosis, and cell polarity (Lisanti el al., 1995; Anderson, 1993a, Anderson, 1993b). More recently, they have been found to be sites where small molecules are concentrated and internalized by a process called potocytosis. Anderson and co-workers (1993) have described the role of caveolae in the receptor-mediated uptake of the essential vitamin 5 methyltetrahydrofolate in a process described to as potocytosis. Furthermore, a growing body of biochemical and morphological evidence indicates that a variety of molecules known to function directly or indirectly in signal transduction are enriched in caveolae. Thus, CAV seem to paly a prominent role in the processing of hormonal and mechanical signals for cells. Indeed, insights gained from studying potocytosis suggest several different ways that this membrane specialization might function to integrate incoming and outgoing cellular messages (Lisanti et al., 1995; Anderson, 1993a, Anderson, 1993b).

One of the most interesting functional aspects of caveolin has been demonstrated in its signal transduction role (Sargiacomo et al., 1993; Li et al., 1995; Chun et al., 1994). Caveolin is a negative modulator of the GTPase activity associated with heterotrimeric G proteins, and of the endothelial cell nitric oxide synthetase. In addition, neurotransmitter and peptide receptors have been detected in caveolae: beta adrenergic receptors, muscarinic receptors histamine H1 receptors, endothelin ET-A receptors, and receptors for EGF and PDGF. Localization of some of these molecules and their related signal transduction components is pharmacologically modulated. For instance, agonist activation of muscarinic receptors leads to their sorting into caveolae. In contrast, occupancy of muscarinic receptors with antagonists inhibits their sorting into caveolae.

Caveolae, clinical relevance. A primary clinical relevance of CAV was immediately inferred from the observation that caveolin, a principal component of the protein coat of caveolae, is a target of the pp60src-kinase. Further demonstration that transformation of NIH 3T3 cells by various oncogenes led to reductions in cellular levels of caveolin (Kloeske et al., 1995), argues strongly in favor of a role of CAV and caveolin in cancer. Indeed, expression of caveolin can lead to inhibition of anchorange-independent cell growth, thus constituting itself as an attractive target for the treatment and control of cancer. The advancements in our knowledge of the molecules transported and expressed in CAV has increased considerably, and has thus far revealed the expression of G-protein, GPI-linked proteins, glycosphingolipids, CD36, RAGE, plasma membrane porin, dystrophin, Rap 1 GTPase, among others. The expression of all of the above has led to their postulated relevance in the pathogenesis of: atherosclerosis, hyperlipidemia, cerebral malaria, diabetic vascular complications, cystic fibrosis, and Duchennes muscular dystrophy.

Summary: *CAV are flask-shaped, invaginations of the plasma membrane with a diameter of 50-100nm. CAV are insoluble in Titron-X-100, and prosess an outer coat with a striated appearance that is abolished by depletion of cholesterol. One of the principal constituents of the organelle is caveolin. In addition, GPI anchored molecules are concentrated in CAV, as well as other molecules which pinpoint to their potential clinical relevance. CAV have a demonstrated role in basic cellular processes, such as transcytosis, potocytosis, cell signaling and in the establishment of cell polarity. Their functional significance is further demonstrated by the host of molecules found expressed in them, and the physilogical biochemical and pharmacological modulation of their biogenesis. The clinical relevance of this new subcellular transport organe!le has been demonstrated in conditions such as cancer, diabetes, vascular diseases and neurodegenerative disorders like Duchennes muscular dystrophy.*

Acknowledgement:

This work is partially supported by NIH grants GMRR033050 to W.l. Silva, and RR03035 to H. Maldonado and P. Sanabria, and GM50695 to H. Maldonado.

References:

1. Anderson, R.G. (1993). Caveolae: where incoming and outgoing messengers meet. Proc Natl Acad Sci U S A 90: 10909-10913.

2. Anderson, R.G. (1993). Plasmalemmal caveolae and GPI-anchored membrane proteins. CurrOpin Cell Biol: 647-652.

3. Brodsky, F.M. 1988. Living with clathrin: Its role in intracellular membrane traffic. Science. 242: 1396-1402.

4. Brown, S.M., R.G.W. Anderson, and L.J. Goldstein. 1983. Recycling receptors: The round-trip itinerary of migrant membrane proteins. Cell 32:663-667.

5. Campbell, C.H., R.E. Fine, J. Squiciarini, and L.H. Rome. 1983. Coated vesicles from rat liver and calf brain contain cryptic mannose-6-phosphate receptors. J. Biol. Chem. 258: 2628-2633.

6. Campbell, C.H., and L. Rome. 1983. Coated vesicles from rat liver and calf brain contain Iysosomal enzymes bound to mannose-6-phosphate receptors. J. Biol. Chem. 258: 13347-13352.

7. Chun, M., Liyanage, U.K., Lisanti, M.P., and H.F. Lodish. 1994. Signal transduction of a G-protein coupled receptor in caveolae: Colocalization of endothelin and its receptor with caveolin. Proc. Natl. Acad. Sci. USA 91: 11728-11732.

8. Glenney, J.R. Jr., and Soppet, D. (1992). Sequence and expression of caveolin, a protein component of caveolae plasma membrane domains phosphorylated on tyrosine in Rous sarcoma virus-transformed fibroblasts. Proc Natl Acad Sci U S A 89: 10517-10521.

9. Helenius, A., M. Marsh, and J. White. 1980. The entry of viruses into animal cells. TIBS 5:104-106.

10. Heuser, E.J., and S.T. Reese. 1973. Evidence for recycling of synaptic vesicle membrane during transmitter release at the frog neuromuscular junction. J. Cell Biol. 57:315 -344.

11. Keen, J.ll., M.C. Willingham, and l.H. Pastan. 1979. Clathrin-coated vesicles: Isolation dissociation and factor-dependent reassociation of clathrin baskets. Cell 16:303-312.

12. Kirchhausen, T., and S.C. Harrison. 1981. Protein organization in clathrin trimers. Cell 23:755761.

13. Koleske, A.J., Baltimore, D., and Lisanti, M.P. (1995). Reduction of caveolin and caveolae in oncogenically transformed cells. Proc Natl Acad Sci U S A: 1381 - 1385.

14. Kurzchalia, T.V., Dupree, P., and Monier, S. (1994). VlP21-Caveolin, a protein of the trans-Golgi network and caveolae. FEBS Lett 346: 88-91.

15. Li, S., Okamoto, T., Chun, M., Sargiacomo, M., Casanova, J.E., Nishimoto, l., and M. P. Lisanti . 1995. Evidence for a regulated interaction between heterotrimeric G proteins and caveolin. J. Biol. Chem. 270:15693-15701.

16. Lisanti, M.P., Tang, Z., Scherer, P.E., Kubler, E., Koleske, A.J., and Sargiacomo, M. (1995). Caveolae, Transmembrane signalling and cellular transformation. Mol Membr Biol 12: 121-124.

17. Lisanti, M.P., L.S. Shapiro, N. Moskowitz, E.L. Hua, S. Puszkin, and W. Schook. 1982. Isolation and preliminary characterization of clathrin associated proteins. Eur. J. Biochem. 125:463470.

18. Lisanti, M.P., Tang, Z., Scherer, P.E., and Sargiacomo, M. (1995). Caveolae purification and glycosyl-phosphatidylinositol-linked protein sorting in polarized epithelia. Methods Enzymol 250: 655-668.

19. Nevorotin, A.J. 1980. Coated vesicles in different cells types: some functional implications. In, Coated Vesicles, edited by Ockleford and Whyte, Cambridge University Press, 1980, p.25-54

20. Orci, L., M. Ravazzola, M.J. Storch, R.G. W. Anderson, J.D. Vassalli, and A. Perrelet. 1987. Proteolytic maturation of insulin is a post-Golgi event which occurs in acidifying clathrincoated secret ary vesicles. Cell 49:865-868.

21. Orci, L., P. Halban, M. Amherdt, M. Ravazzola, J-D Vasalli, and A. Perrelet.1984. Non-converted amino acid analog-modified proinsulin stays in a Golgi derived clathrin-coated membrane compartment. J. Cell. Biol. 99:2187-2192.

22. Palade GE(1953) Fine structure of blood capillaries. J Appl Physics 24:1424.

23. Palade, G.E., Bruns, R.R. (1968) Structural modulation of plasmalemmal vesicles. J. Cell Biol 37:633-649.

24. Pearse, B.M.F. 1976. Clathrin: a unique protein associated with intracellular transfer of membrane by coated vesicles. PNAS 73:1255-1259.

25. Pearse, B.M.F. 1978. Clathrin: On the structural and functional components of coated vesicles J. Mol. Biol. 126: 803-812.

26. Pearse, B.M.F. 1982. Coated vesicles from human placenta carry ferritin, transferrin and immuno-globulin G. PNAS 79: 451455.

27. Rothberg, K.G., Heuser, J.E., Donzell, W.C., Ying, Y.S., Glenney, J.R., and Anderson, R.G. (1992). Caveolin, a protein component of caveolae membrane coats. Cell 68: 673-682.

28. Sargiacomo, M., Sudol M, Tang Z-L, Lisanti, M.P. (1993) Signal transducing molecules and glycosyl-phosphatidylinositol-linked proteins form a caveolin rich insoluble complex in MDCK cells. J Cell Biol 122:789-807.

29. Sargiaomo, M., Scherer, P., Tang, Z.-L., Kubler, E., Song, K., Sanders, M., and M.P. Lisanti. 1995. Oligomeric structure of caveolin: Implications for caveolae membrane organization. Proc. Natl. Acad. Sci. USA 92:9407-9411.

30. Schook, W.J., S. Puszkin, W. Bloom, C. Ores, and S. Kochwa. 1979. Mechanochemical properties of brain clathrin: interaction with actin and alpha-actinin and polymerization into basket-like structures or filaments. PNAS 76: 116-120.

31. Smart, E.J., Ying, Y.S., and Anderson, R.G. (1995). Hormonal regulation of caveolae internalization. J. Cell Biol. 131: 929-938.

32. Tang, Z.-L., Scherer, P.E., and M.P. Lisanti. 1994. The primary sequence of murine caveolin reveals a conserved consensus site for phosphorylation by protein kinase C. Gene 147:299-300.

33. Tooze, J., and S.A. Tooze. 1986. Clathrincoated vesicular transport of secretary proteins during the formation of ACTH-containing secret ary granules in AtT20 cells. J. Cell Bol. 103: 839-850.

34. Unanue, E.R., E. Unge wickel, and D. Branton. 1981. The binding of clathrin triskelions to membrane coated vesicles. Cell 26: 439-446.

35. Ungewickel, E., and D. Branton. 1981. Assembly units of clathrin coats. Nature 289:420 -422.

36. Woodward, M.P., and T.F. Roth. 1978. Coated vesicles: characterization, selective dissociation, and reassembly. PNAS 75:4394-4398.

Reporte de Casos:

Acute Appendicitis: As a predisposing factor for acute glomerulonephritis - Report of two cases

*Juan I. Camps M.D., Víctor N. Ortiz, M.D. FACS. FAAP**
*Anthony Bufo, M.D., Thom E. Lobe M.D. FACS. FAAP***

***Abstract:** This is a review of two children who developed acute glomerulonephritis (AGN) following acute gangrenous appendicitis (AGA) with periappendicular collections. The first patient presented with AGN during the course of appendicitis. The second patient developed AGN after appendectomy. Both patients did not have any other predisposing factors. AGN resolved in both patients after massive intravenous antibiotics. This is the first report of acute appendicitis as a predisposing factor for AGN.*

Key Words
Acute appendicitis, Acute glomerulonephritis.

Introduction:

As a general concept, acute glomerular disease generally presents as either a nephritic syndrome witll facial swelling, hematuria, granular cast in the urine and hypertension, or as a nephrotic syndrome with gross proteinuria, acute or chronic renal failure and hypertension. Renal biopsy is ussually necessary in order to reach a precise diagnosis of the type of glomerulonephritis involved. Glomerular injury may be the result of inmunologic, infectious or coagulation dlsorders. Inmunologic injury is a common cause and results in glomerulonephritis. In inmune complex-mediated diseases, antibody is produced against and combines with a circulating antigen that is ussually unrelated to the kidney. The inmune complexes accurnulate in glomeruli and activate the complement system, leading to inmune injury.

Proliferation of glomerular cells occurs in most forms of glomerulonephritis, involving all glomeruli, or focal, involving only some glomeruli while sparing others. Within a single glomerulus, proliferation may be diffuse, or segmental. Proliferation also involves the endothelial and mesangial cells. The IgA Glomerulonephritis is believed to be the most common form of primary glomerular disease throughout the world, however it is seen only in about 10 percent of all renal biopsies performed in North America. There are many predisposing factors including septic foci anywhere in the body.

CASE REPORT: PATIENT# 1.

A 10 years old white male patient presented with abdominal pain, nausea, vomiting and hematuria for four days. The patient had history of hematuria and oliguria. There was no history of allergies to drugs. On examination there was a distended abdomen with diffuse tenderness. The patient had nocturnal enuresis, which was well controlled with Methylphenidate 10 mg. PO bid.

There was a Leukocytosis of 28,400 cells per cubic mm with 85% neutrophils. The renal parameters showed BUN of 41mg/dl and Creatinine of 2.2mg/dl. The urinalysis revealed the following findings: a cloudy urine with a specific gravity of 1.025, pH-5, traces of Leukocytes, Protein 2+, Blood 3+ with 25-50 red blood cells per hpf and few red cell casts and few granular casts. The total protein was 6.3gm/dl with an Albumin of 3.2gm/dl and A/G ratio of 1.3. The coagulation profile was within normal limits. Plain roentgenograms revealed the presence of fluid levels and no free air. Ultrasound and Computed tomography showed a right lower quadrant liquid collection suggestive of abscess formation.

The patient was started on intravenous antibiotics: ampicillin lgm. q. 12 hrs; gentamycin 1.5 mg/kg q. 12 hrs and clindamycin 150 mg q. 6 hrs. He was given 20 ml/kg of bolus fluid before surgery. On exploratory celiotomy he was found to have gangrenous appendicitis with abscess formation. He underwent appendectomy and irrigation of the abscess cavity. Post operative recovery was slow with fever for 7 days, which went back to normal, and the patient was discharged on his 10th post operative day. Renal

**From the General Surgery Department, Mayaguez Medical Center, Mayaguez, P.R.*
***From the Pediatric Surgery Department, Le Bonheur Children's Medical Center, Memphis. TN*
****Ponce School of Medicine*
All correspondence with: Víctor N. Ortiz M.D., PO Box 3008, Mayaguez, P.R.

biopsy with electron microscopy confirmed it to be an IgA nephropathy with focal segmental mesangial proliferative glomerulonephritis with acute tubular necrosis. The patient had normal renal function at the time of discharge.

PATIENT# 2:

A 14 years old white male patient was transferred from an outlying hospital after developing AGN, after appendectomy. He had abdominal pain, vomiting and hematuria of three days duration. He had an upper respiratory tract infection one week prior to surgery. There was no history of allergies. On examination, the oropharinx was mildly erythematous without any mucosal exudate and there was no cervical lymphadenopathy.

A rapid streptococcal screen antigen and culture were negative. The patient had a White Blood Cell count of 13,500/mm3 with a segmental cell count of 83%. The blood urea nitrogen was 17 mg/dl and the serum creatinine was 1.1 mg/dl. The total protein was 5.9 gm/dl with an albumin of 3.2 gm/dl and A/G ratio of 1.2. The coagulation profile was within normal range. The urinalysis revealed a cloudy urine with pH of 6, 2+ proteinuria, Red Blood Cell casts, 3+ blood, 1-3 granular casts, 3+ bacteria and hyaline casts. The intravenous urography showed normal functioning of both Kidneys.

He was started on intravenous Ceftazidime 2 gms g. 12 hrs. and Clindamycin 300 mgs q. 6 hrs. He underwent cystoscopy which showed continuos flow of bloody urine from both ureteric orifices.

He gradually recovered and was discharged after eight days. He had a normal renal function and the urine analysis was normal. The renal biopsy showed it to be a IgA nephropathy with dense deposits occupying the lateral position on the mesangium.

DISCUSSION

There are many predisposing conditions leading to IgA nephropathy including Schonlein-Henoch Purpura, carcinoma of the respiratory tract, chronic liver disease, and sepsis due to any cause.[1-2]

The described infectious etiology includes leprosy, toxoplasmosis, HIV infection and acute tonsillitis. (Table-1). The idiopathic presentation form is well known as Berger's Disease. The clinical spectrum of presenting symptoms is variable. The diagnosis is achieved by renal biopsy in a patient with recurrring episodes of macroscopic hematuria. The renal biopsy shows presence of dense deposits predominantly consisting of IgA and C3 in the glomerular mesangium. The exact mechanism is not yet well defined. The circulating IgA immunocomplexes are increased in the pathologically inflammed tissues, rich in immunoglobin such as respiratory and gastrointestinal mucosa.

TABLA 1:
GLOMERULONEFRITIS

1. STREPTOCOCCUS
2. NON-STREPTOCOCCUS

- BACTERIA: Infiectious endocarditis
  Atrio-Ventricular shunts
  Systemic sepsis
  Pneumonia (Staphylococcus, Klebsiella...)
- VIRUSES: Hepatitis B
  Cytomegalovirus
  Herpes virus
- FUNGUS: Histoplasmosis

Acute glomerulonephritis secondary to a septic focus still represents a common etiology of the acute renal syndromes[3]. The leading cause is Beta-hemolytic Streptococcus infection[1]. The other organisms related to this condition are staphylococcus[8], pneumococcus and viruses. The AGN is known to occur following infective endocarditis[4], shunt nephritis[5] and chronic bacterial pyelonephritis. In all these conditions an immunologic mechanism has been implicated. The electron microscopy with immunofluorescence reveals a patern of multiple focal density due to deposition of multiples inmunocomplexes. (Figure 1-2)

Thus far, acute appendicitis is not reported as a predisposing condition for IgA nephropathy. In both the reported patients acute appendicitis lead to AGN. Intraabdominal abscesses have been reported as a cause of acute glomerulonephritis in adults[6-7]. There is a single report of AGN caused by intraabdominal abscesses in children[3].

The exact pathogenesis is difficult to ascertain but it is probably related to antigens of the organisms involved in acute appendicitis. In both patients effective treatment was started early and hence exposure to the causative antigen was limited. The aggresive management of both patients led to the formation of a small quantity of immune complexes and to an eventual early recovery.

The findings suggestive of poor prognosis include diffuse proliferative glomerulonephrits, especially when it is accompained by segmental or diffuse crescent sclerosis and interstitial fibrosis or proteinurias



Figure 1: Electron micrograph of IgA nephropathy. There is thickening of the mesangial area containing numerous electron-dense deposits x 4660. The capillary loops are normal. Mesangiocapillary glomerulonephritis.



Figure 2: Inmunofluorescence microscopy of IgA nephropathy. The section shows accumulation of IgA-containing deposits in the mesangial region of a glomerulus.

over 1 gm/dl. The overall prognosis of IgA nephropathy is favorable. Usually only the treatment of the precipitating factor is required to treat the IgA nephropathy. However, the complicated cases may require treatment with steroids and, or cytotoxic agents.

Resumen: *La manifestación de la glomerulonefritis aguda secundaria a procesos infecciosos o inmunes son a menudo discretas y la afección renal a menudo solo se manifiesta por proteinuria y hematuria. La biopsia renal muestra por lo general una glomerulonefritis proliferativa endocapilar difusa o segmentaria y focal. En la mayoría de los casos la recuperación clínica e histológica es satisfactoria. Este es el caso de dos pacientes pediátricos con afección renal secundaria a apendicitis aguda. La evolución clínica resolvió luego de antibióticos endovenosos y apendicectomia.*

REFERENCES

1. Luther B. Travis. Rudolph's Pediatrics Textbook: 20ed. 1996. IgA Nephropathy chapter.1359-60.

2. Glassock, Cohen and Adler: Pathogenesis of renal disease textbook. IgA Nephropathy. Chapter30, 1995; 1414-21.

3. Beaufilset, Morel-Maroger, Sraer et al: Acute renal failure of glomerular origin during visceral abscesses. N England J Med 1976; 295: 185-89.

4. Keslin MH, Messner RP, Williams RC Jr. Glomerulonephritis with subacute bacterial endocarditis. Arch Intern Med 1973: 132: 578-81.

5. Stickler GB, Shin MII, Burke EC et al. Diffilse glomerulonephritis associated with infected ventriculo-atrial shunt. N England J Med 1968; 279: 1077-82.

6. Acute renal failure in minimal change nephrotic syndrome. Pediatric vol 80. The Children's Hospital of Buffalo. Division of Pediatric Nephrology.

7. Lowenstein J, Schacht RG, Baldwin DS. Renal failure in minimal change nephrotic syndrome. Am J Med 1981, 70: 227-233.

8. Tu WH, Shearn MA, Lee JC, et al. Acute diffuse glomerulonephritis in acute staphylococcal endocarditis. Ann Intern Med 1969; 71: 335-341.



Si usted está en la menopausia, podría estar desarrollando osteoporosis. Aliviar los síntomas de la menopausia puede ayudarla a sentirse mejor y proteger su futuro contra la osteoporosis. Pregúntele a su doctor sobre PREMPRO.

Si usted está en la menopausia, en su cuerpo están ocurriendo cambios. Cambios que no sólo le afectan ahora si no que podrían afectar significativamente su futuro. Los sofocones, sudoraciones nocturnas y la resequedad vaginal que pudiera estar experimentando son el resultado de que su cuerpo produce menos y menos estrógeno. La terapia de reemplazo hormonal con PREMPRO puede aliviar estos síntomas y ayudarle a sentirse mejor.

Usted puede estar perdiendo masa ósea... en este momento.

La menopausia también marca el tiempo en su vida cuando, debido a la pérdida de estrógeno, comienza a perder masa ósea más rapidamente. De hecho, la mitad de la masa osea que la mujer pierde, ocurre entre los primeros 3 a 6 años de comenzada la menopausia. Para algunas mujeres, la pérdida de masa ósea puede llevar a osteoporosis, una enfermedad seria que afecta a una de cada cuatro mujeres sobre los 50. Pregunte a su doctor acerca de los factores de riesgo de la osteoporosis para ayudarle a determinar si usted está en riesgo.

Aún cuando el calcio, la dieta y el ejercicio son importantes para mantener huesos fuertes, estos pueden no ser suficientes para ayudar a prevenir la osteoporosis. Por esta razón, muchos doctores recetan PREMPRO para mujeres que no han tenido una histerectomía.

PREMPRO es una terapia de reemplazo hormonal de dosis baja o HRT y es la única combinación de estrógeno y progestina disponible en una sóla tableta.

PREMPRO combina los estrógenos de PREMARIN® (tabletas de estrógenos conjugados, USP), el estrógeno tomado por mas de 9,000,000 mujeres americanas, con progestina... en una conveniente tableta.

Aün cuando algunas mujeres que toman PREMPRO pueden experimentar sangramiento de tipo menstrual, investigaciones han demostrado que muchas mujeres tomando PREMPRO dejan de sangrar después de un año de uso.

Mujeres tomando PREMPRO podrían experimentar un aumento en sus lipoproteinas de alta densidad (HDL's), generalmente conocido como "colesterol bueno", aunque este efecto es menor que cuando toman PREMARIN sola. PREMPRO también disminuye las lipoproteinas de baja densidad (LDL's), generalmente conocidas como "colesterol malo". Este efecto es comparable a PREMARIN solo. Asegúrese de hablar con su doctor acerca del perfil de su colesterol.

Menopausia: una época para mirar hacia adelante

Los efectos secundarios de las hormonas deben considerarse.

Si usted no ha tenido una histerectomía, el estrógeno solo puede aumentar el riesgo de cáncer de útero. La adición de la progestina reduce grandemente este riesgo. Es por eso que muchos doctores y proveedores de salud ahora recetan progestina con estrógeno a sus pacientes. La progestina puede traer efectos adversos en las azúcares de la sangre, lo que podría agravar una condición diabética. Los efectos secundarios más comunes de la terapia de reemplazo hormonal son sensibilidad en los pechos, dolor de cabeza y dolor abdominal.

Cuando usted hable con su doctor o proveedor de salud acerca de la terapia de reemplazo hormonal , asegúrese de discutir su historial personal o familiar de cáncer de las mamas, masas en los senos, sangramiento vaginal anormal, coagulación anormal de la sangre, dolores de cabeza agudos, mareos o enfermedad del hígado. Mujeres en estado de embarazo no deben tomar terapia de reemplazo hormonal debido a posibles riesgos al feto.

Ayude a proteger su futuro contra la osteoporosis. Hable con su médico acerca de los efectos a largo plazo de la menopausia, tales como la osteoporosis.

Hoy, más mujeres que nunca antes están tomando un rol activo en el cuidado de su salud. ¿Por qué no ayudar a proteger su futuro contra la osteoporosis?

Hable con su doctor o proveedor de salud. Pregunte por PREMPRO, la terapia de reemplazo hormonal de dosis baja que se ha comprobado alivia síntomas de la menopausia y que ayuda a prevenir la osteoporosis. Se sentirá mejor.

Asegúrese de leer información importante en la próxima página.

Asegúrese de leer información importante en la próxima página.



Pregunte a su médico.

BREVE RESUMEN DE INFORMACIÓN SOBRE PRESCRIPCION PARA EL PACIENTE

Tabletas PREMPRO(TM) de estrógenos conjugados/acetato de medroxiprogesterona.
Este resumen describe cuándo y cómo usar fármacos de estrógeno/progestina y los beneficios y riesgos del tratamiento.

LOS FÁRMACOS DE ESTRÓGENO/PROGESTINA

PREMPRO es una combinación de dos hormonas, un estrógeno y una progestina. Se ha comprobado que esta combinación de hormonas provee los beneficios de las terapias de reemplazo de estrógeno al mismo tiempo que disminuye la frecuencia de una posible condición precancerosa de la capa uterina interior. Esta terapia no es para usarse en mujeres que han tenido una histerectomía (extirpación quirúrgica del útero). Los estrógenos tienen varios usos importantes, pero también algunos riesgos. Usted deberá decidir, con su médico, si los riesgos de los estrógenos resultan aceptables al compararlos con los beneficios. Consulte con su médico para cerciorarse de que esté usando la dosis efectiva más pequeña posible.

La terapia de PREMPRO puede producir varios patrones de sangrado parecidos a la menstruación. Estos patrones pueden fluctuar desde una ausencia de sangrado hasta un patrón irregular de sangrado. De ocurrir algún sangrado, el mismo a menudo consiste en manchas leves o en sangrado parecido al de una menstruación moderada, aunque podría ser abundante. Discuta su patrón de sangrado con su médico y determine un calendario apropiado para el cuidado de seguimiento.

USOS DEL ESTRÓGENO

Para reducir los síntomas de la menopausia. Los estrógenos son hormonas producidas por los ovarios de mujeres normales. La disminución en la cantidad de estrógeno ocurre en todas las mujeres, usualmente entre las edades de 45 y 55, provoca la menopausia. En ocasiones se remueven los ovarios como parte de una operación provocándose una "menopausia quirúrgica". Cuando la cantidad de estrógeno comienza a disminuir, algunas mujeres desarrollan síntomas muy incómodos, como sensación de calor en la cara, el cuello y el pecho o episodios súbitos de calor y sudor ("calentones" o "sofocones"). El uso de fármacos de estrógeno pueden ayudar al cuerpo a ajustarse a los niveles más bajos de estrógeno y reducir estos síntomas. Algunas mujeres no experimentan ningún síntoma de menopausia o tienen síntomas muy leves; en otras los síntomas pueden ser severos. Estos síntomas pueden durar unos meses solamente o más tiempo. PREMPRO puede aliviar estos síntomas. Si usted no está tomando hormonas por otras razones, como puede ser la prevención de la osteoporosis, debería tomar PREMPRO todo el tiempo que sea necesario para el alivio de los síntomas de la menopausia.

Para evitar huesos quebradizos. Después de los 40 años y especialmente después de la menopausia, algunas mujeres desarrollan osteoporosis. Esta condición hace que los huesos pierdan densidad, debilitándose y haciéndose más propensos a romperse, con fracturas frecuentes de la columna vertebral, las caderas y los huesos de la muñeca. La terapia de estrógenos luego de la menopausia retrasa la pérdida ósea y puede evitar que se rompan los huesos. La ingestión de alimentos altos en calcio (productos lácteos, por ejemplo) o de suplementos de calcio (de 1000 a 1500 miligramos diarios) y ciertos tipos de ejercicios también pueden ayudar a prevenir la osteoporosis. Dado que el uso de estrógeno va asociado con algunos riesgos, su uso en la prevención de la osteoporosis debe limitarse a mujeres que parecen ser propensas a esta condición. Las mujeres con probabilidad de desarrollar osteoporosis a menudo exhiben estas características: blancas o asiáticas, delgadas, fumadoras, con historial familiar de osteoporosis o menopausia temprana o quirúrgica.

Para tratar la atrofia vulvar o vaginal (picor, ardor, resequedad en o alrededor de la vagina, dificultad o ardor al orinar) asociada con la menopausia.

CUANDO NO DEBE USARSE EL ESTRÓGENO

Durante el embarazo (véase la Advertencia del Recuadro). Si usted tiene motivos para pensar que está embarazada, no tome ninguna clase de fármaco que contenga estrógeno. Si usa estrógeno mientras está embarazada podría hacer que su bebé nazca con defectos congénitos. Los estrógenos no evitan el aborto espontáneo.

Si tiene sangrado vaginal inusual que no ha sido evaluado por su médico (véase la Advertencia del Recuadro). El sangrado vaginal inusual puede ser una señal de aviso de cáncer uterino, especialmente si ocurre luego dela menopausia. Su médico deberá descubrir la causa del sangrado para poder recomendar el tratamiento adecuado. Tomar estrógenos sin visitar a su médico puede ocasionar un daño severo si el sangrado vaginal es causado por cáncer del útero.

Si ha tenido cáncer. Dado que los estrógenos aumentan el riesgo de ciertos tipos de cáncer, no debe usarlos si ha tenido alguna vez cáncer de mamas o del útero.

Si tiene algún problema circulatorio. Los fármacos con estrógeno no deben usarse excepto en situaciones especiales insólitas en las cuales su médico decida que su necesidad de terapia de estrógeno es tan grande que los riesgos resultan aceptables. Las mujeres con anomalías en la coagulación deben evitar el uso de estrógenos, (véase **RIESGOS DE LOS ESTRÓGENOS Y/O LAS PROGESTINAS**).

Cuando no funcionan. Durante la menopausia, muchas mujeres desarrollan síntomas nerviosos o depresión. Los estrógenos no alivian estos síntomas. Puede haber escuchado que tomar estrógeno durante años luego de la menopausia mantendrá su piel suave y flexible y hará que se siga sintiendo joven. No hay prueba de que esto es cierto y dicho uso de estrógeno por largo tiempo puede conllevar riesgos serios.

Después del alumbramiento o durante la lactancia. El estrógeno no debe usarse para evitar que las mamas se llenen de leche luego de nacer el bebé. Dicho tratamiento puede aumentar, el riesgo de desarrollar coágulos de sangre. (vease **RIESGOS DE LOS ESTRÓGENOS Y/O LAS PROGESTINAS**).

Si está lactando, debe evitar usar cualquier fármaco ya que muchos fármacos pasan al bebé en la leche. Mientras lacta al bebé sólo debe tomar los fármacos que le recomiende su proveedor de cuidados de salud.

RIESGOS DE LOS ESTRÓGENOS Y / O LAS PROGESTINAS

Cáncer del útero. El riesgo de cáncer del útero aumenta cuando los estrógenos se usan solos, cuanto más tiempo se usen y cuando se toman en dosis altas. Existe un riesgo mayor de cáncer del útero si usted está sobrepeso, es diabética o padece de hipertensión.

La combinación de hormonas que va a tomar contiene estrógeno y progestina. Se ha comprobado que esta combinación brinda los beneficios de la terapia de remplazo de estrógenos al mismo tiempo que reduce el riesgo de una condición precancerosa de la capa uterina interior.

Pueden existir otros riesgos asociados con la inclusión de la progestina en el tratamiento de estrógenos. Los posibles riesgos incluyen efectos desfavorables en los lípidos y azúcares sanguíneos. Generalmente cuanto menor la dosis y más corta la duración del tratamiento, mayor es la minimización de estos síntomas. Consulte con su médico para cerciorarse de que está tomando la dosis efectiva más pequeña y sólo por el tiempo que la necesite.

Cáncer de mamas. La mayoría de los estudios no ha demostrado un riesgo mayor de cáncer de mamas en mujeres que han usado estrógeno alguna vez. No obstante, algunos estudios han informado un desarrollo más frecuente de cáncer de mamas (hasta el doble de la tasa usual) en mujeres que usaron estrógenos por periodos largos (particularmente más de 10 años) o que usaron dosis altas por periodos más cortos. Se desconocen los efectos de añadir la progestina sobre el riesgo de desarrollar cáncer de mamas. Algunos estudios han informado cierto aumento en el riesgo, aún más alto que el posible riesgo asociado con los estrógenos solos. Otros no han informado nada. Se recomiendan exámenes regulares de las mamas por un profesional de la salud y autoexámenes mensuales para todas las mujeres.

Enfermedad de la vesícula. Las mujeres que usa estrógenos después de la menopausia tienen mayor probabilidad de desarrollar enfermedad de la vesícula que requiera cirugía que las mujeres que no usan estrógenos.

Inflamación del páncreas. Las mujeres con niveles de triglicéridos pueden tener un riesgo mayor de desarrollar inflamación del páncreas.

Anomalía de coagulación. Tomar estrógenos puede aumentar el riesgo de coágulos. Estos coágulos pueden causar accidentes cerebrovasculares, ataques cardiacos o embolia pulmonar, cualquiera de los cuales puede causar la muerte o una incapacidad severa por largo tiempo.

Exceso de calcio en la sangre. Tomar estrógenos puede producir hipercalcemia severa en mujeres con cáncer de mamas y/o de los huesos.

Durante el embarazo. Hay un aumento en el riesgo de defectos congénitos en bebés cuyas madres toman este fármaco durante los primeros cuatro meses del embarazo. Varios informes sugieren una relación entre la madres que toman estos fármacos durante el primer trimestre del embarazo y anomalías genitales en bebés, tanto hembras como varones. El riesgo para los varones es la posibilidad de nacer con una condición en la cual la apertura del pene se encuentra en la cara inferior del pene en vez de en la punta (hipospadias). La hipospadias ocurre en unos 5 a 8 por cada 1,000 nacimientos esta tasa casi se dobla con la exposición a estos fármacos. No existe suficiente información para cuantificar el riesgo a los fetos femeninos expuestos. No obstante, puede ocurrir agrandamiento del clítoris y función de los labios, aunque rara vez.

Por tanto, dado que los fármacos de este tipo pueden inducir una masculinización leve de los genitales externos del feto femenino, así como hipospadias en fetos masculinos, es prudente evitar el uso de este fármaco durante el primer trimestre del embarazo. Estos fármacos se han utilizados para pruebas de embarazo, pero dicho uso ya no se considera seguro por el posible daño al bebé en desarrollo. Además, ya hay métodos más rápidos disponibles para pruebas de embarazo. Si toma PREMPRO y luego descubre que estaba embarazada cuando lo tomó, no deje de informarlo a su médico lo antes posible.

EFECTOS SECUNDARIOS DE LOS ESTRÓGENOS Y LAS PROGESTINAS

Además de los riesgos mencionados anteriormente, se han informado los siguientes efectos secundarios con el uso del estrógeno y/o la progestina:

- Náusea, vómitos, dolor, calambres, hinchazón o sensibilidad en el abdomen.
- Amarillez de la piel y/o el blanco de los ojos.
- Agrandamiento o sensibilidad de las mamas.
- Agrandamiento de tumores uterinos benignos.
- Sangrado o manchado irregular.
- Cambio en la cantidad de secreción cervical.
- Infecciones vaginales por hongo.
- Retención excesiva de líquido. Esto puede empeorar algunas condiciones tales como el asma, la epilepsia, la migraña, las enfermedades cardiacas o las enfermedades renales.
- Manchas oscuras en la piel, en la cara sobre todo; enrojecimiento de la piel, erupciones cutáneas
- Empeoramiento de la porfiria.
- Dolores de cabeza, migrañas, mareos, desmayos o cambios en la visión (intolerancia a lentes de contacto inclusive).
- Depresión mental
- Espasmos musculares involuntarios.
- Caída del cabello o hirsutismo anormal.
- Aumento o pérdida de peso.
- Cambios en el impulso sexual.
- Posibles cambios en el azúcar sanguínea.

COMO REDUCIR LOS RIESGOS DEL USO DE ESTRÓGENOS/PROGESTINAS

Si usted decide tomar una combinación de estrógeno y progestina, puede reducir los riesgos vigilando cuidadosamente el curso del tratamiento. Visite a su médico regularmente. Mientras esté tomando PREMPRO, es importante que visite a su médico para un chequeo al menos una vez al año. Si desarrolla sangrado vaginal mientras toma estrógenos, puede necesitar una evaluación adicional. Si algún familiar ha tenido cáncer de mamas o si usted ha tenido alguna vez tumores en las mamas o una mamografía (placa de mamas) anormal, podría necesitar exámenes más frecuentes en las mamas.

Reevalúe su necesidad de tratamiento. Usted y su médico deberán reevaluar la necesidad de estrógenos al menos de cada seis meses. Manténgase alerta a cualquier señal de problemas. Informe los síntomas que siguen, así como cualquier otro síntoma inusual, a su médico inmediatamente:

- Sangrado vaginal anormal.
- Dolores en la pantorrillas o el pecho, dificultad súbita para respirar o toser sangre.
- Dolor de cabeza severo o vómitos, mareos, desmayos o cambios en la visión o el habla, debilidad o adormecimiento de un brazo o una pierna.
- Masas en las mamas.
- Amarillez en la piel y/o el blanco de los ojos.
- Dolor, hinchazón o sensibilidad en el abdomen.

OTRA INFORMACIÓN

Los estrógenos aumentan el riesgo de desarrollar una condición (hiperplasia del endometrio) que puede producir cáncer de la capa uterina interior. Tomar progestinas, otro fármaco hormonal, junto con estrógenos disminuye el riesgo de desarrollar esta condición. Debe saber, sin embargo, que tomar estrógenos con progestina podría tener efectos no saludables sobre el azúcar sanguínea lo cual podría empeorar una condición de diabetes. Algunas investigaciones han demostrado que tomar estrógenos sin progestinas podría proteger a las mujeres de enfermedades cardiacas. Sin embargo, esto no puede asegurarse. Se ha demostrado que esta protección podría responder a las características de las mujeres tratadas con estrógenos y no al tratamiento de estrógenos en sí. En general, las mujeres tratadas, eran más delgadas, estaban más activas físicamente y tenían menor probabilidad de tener diabetes que las mujeres no tratadas. Se sabe que estas características protegen contra las enfermedades cardiacas. Es importante discutir en detalle con su médico o su proveedor de cuidado de salud, todos los posibles riesgos y beneficios del tratamiento a largo plazo con estrógeno y progestina ya que los mismos la afectan a usted personalmente. Este resumen brinda la información más importante acerca de PREMPRO. Si desea leer más sobre este tema, pida a su médico o farmacéutico que le permita leer la información en la etiqueta profesional. Este Breve Resumen para Publicidad Directa al Consumidor se basa en el inserto actual (PI 4665-1) de las Tabletas PREMPRO emitido el 19 de enero de 1998, con la incorporación de lenguaje lego en el texto pertinente del inserto para el Médico (CI4664-4) emitido el 19 de enero de 1998.



Reporte de Casos:

Unusual Case of Meckel's Diverticulum:

A Case Report and Review of an atypical form of presentation

*Juan I. Camps MD. Victor N. Ortiz MD. FACS. FAAP**
*Anthony Bufo MD, Thom E. Lobe MD. FACS. FAAP***

Abstract: This is a review of a child who developed symptomatic anemia secondary to a huge Meckel's Diverticulum (MD). The patient presented with multiple complications, such as: neoplasia, occult chronic bleeding, giant size MD, partial intestinal obstruction and severe symptomatic anemia. There was complete resolution of the condition after resection and ileo-ileal anastomosis. After revision of the literature, this case is the first report of MD occurring concomitanly with such a myriad of signs and symptoms.

KEY WORDS:
Meckel's Diverticulum, Neoplasia, Giant size.

Meckel's Diverticulum results from failure of complete obliteration of the vitelline or omphalomesenteric duct during the fifth embrionic week. In cases of failure of obliteration of the duct over its entire course a fistula result from the small bowel to the umbilicus. When there is obliteration of the omphalic side the result is MD. The most common clinical presentations are: lower gastrointestinal bleeding, intestinal obstruction, and diverticulitis[1]. The usual source of the bleeding is a chronic ileal ulcer associated with heterotopic gastric tissue within the diverticulum. Bleeding usually present as melena or bright red. The cause of intestinal obstruction is related to a volvulus of the small bowel around the diverticulum that is attached to the anterior abdominal wall, intussusception or encarceration of the diverticulum in a hernia (Littre). In case of diverticulitis, often presented as acute appendicitis, may lead to perforation of the diverticulum.

The large size of the diverticulum, the presence of occult blood, the severe symptomatic anemia and the findings of leiomyoma in the same patient represents a unique case. Its clinical significance will be discussed, together with a pertinent review of the english literature.

CASE HISTORY:

A 16 years-old black male patient was admitted to our institution with complains of severe fatigue, shortness of breath and general malaise for the past two weeks. He had several examinations over the last six months due to vague abdominal cramps, intermitent vomiting and weight loss (5-10 lbs.). The past medical history was unremarkable. He had three episodes of rectal bleeding prior to admission. On physical examination, he looked severely dehydrated and pale. No lymphadenopathy was found. On auscultation, the lungs were clear but he had tachycardia with an ejection murmur. The abdomen was very distended and tympanic with asymmetry of the back. Rectal examination was negative for masses or occult blood. An abdominal CT-Scan revealed a large cystic mas that filled almost completely the abdominal cavity and extended into the pelvis (see Figure 1-2), with 24 cm. in its greatest dimension. Bilateral hydronephrosis was encountered with the small bowel and transverse colon displaced cephalad. The laboratories on admission were: Hb: 4.1 gm/dl , Hct: 14.4 %, normal coagulation tests, total protein 7.7 gm./dl and albumin 4.0 gm/dl. He underwent an exploratory celiotomy after transfusion of five units of pack red blood cells. Operative findings were of a 21 x 20 x 9 cms, soft cystic mass filled with a brown liquid with red blood cells and white blood cells detritus. A firm mass excrescence in the interior of the cyst that measured 12 x 10 x 9 cm. was reported as a leiomyoma. The cyst emerged from the antimesenteric border of the distal ileum. A partial small bowel resection with side to side stapled anastomosis was performed. The patient was discharged seven days after surgery without complications.

DISCUSSION:

MD is the most prevalent congenital anomaly of the gastrointestinal tract.[2] Occurs in approximately

* *From the General Surgery Department, Mayaguez Medical Center, Mayaguez.PR*
** *From the Pediatric Surgery Department, Le Bonheur Children's Medical Center, Memphis.TN*
All correspondence with: Victor N. Ortiz MD, PO BOX 3008. Mayaguez. PR

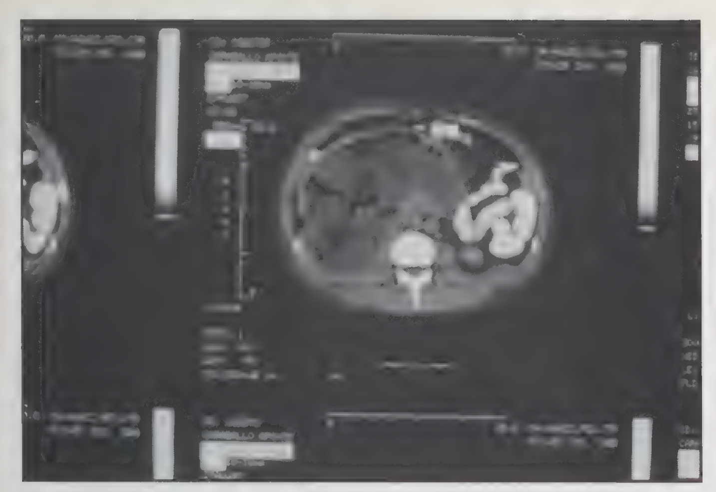


Figure 1.

two percent of the population and may present at any age. There is sex predominance of 1.7 males per each female. This male predominance is almost twice as much when only symptomatic patients are considered[3,4].

Symptomatic MD is most frequent seen in early childhood. Only 16.9 % of all MD are symptomatic. Most cases are diagnosed at autopsy, followed by exploratory celiotomy for other reasons.[5] (see Table1)

TABLE 1
PREVALENCE OF MECKEL'S DIVERTICULUM

CONDITION	
AUTOPSY	45.1 %
EXPLORATORY LAPAROTOMY	34.9 %
SYMPTOMATIC CASES	16.9 %
ROENTGENOGRAPHIC	1.5 %

The lenght of MD is usually 5-6 cm.,[6] but it can be gigantic as in our case.[7] Lenght is a determinant factor for development of symptoms, the longer it is the higher the possibility of having symptoms. Patient's age, presence of heterotopic mucosa and sex are also important factors for the development of complications. Young, male patient have a much higher incidence of becoming symptomatic. The presence of occult blood in MD is rare. Chronic blood loss with development of iron deficit anemia is even rarer[8-9]

Although the normal epithelium of the diverticulum is ileal mucosa, heterotopic gastric, pancreatic, jejunal and colonic tissue can also be found. Gastric heterotopic tissue is the commonest type.[10] With the presence of heterotopic mucosa in the diverticulum the likelihood of symptoms is greater. In cases of incidentally found MD during exploratory celiotomy anatomic findings such as submucosal or mucosal nodules, peridiverticulitis, scarring or inflamatory adhesions should make one suspicious of the presence of heterotopic mucosa.

Neoplasia development in MD is extremely infrequent. [4-6] Benign neoplasms can be divided into those originating from connective tissue, smooth muscle, fatty tissue, nervous tissue, and blood vessel. There is an overall predominance in males.[11] Those tumors arising from the conective tissuehave predominance in males, asymptomatic when the tumor acts as a leading point in intussusception, volvulus, mechanical blockage and inflamatory reaction. In case of tumors with smooth muscle tissue, Leiomyoma is the typical form of presentation. Symptoms are secondary to hemorrhage, ulceration or perforation to the free abdominal cavity. Vascular tumors are very uncommon, Hemangioendotheliomas and Cavernous Hemangiomas. Those arising from the nervous tissue come from the Meissner's and Auerbach's plexus. Fatty tumor present in MD is very rare.

In regard to malignant tumors arising from MD, carcinoid[12], leiomyosarcoma[13] and adenocarcinoma[14], it must be mention that they have poor prognosis. Carcinoid tumors arise from the cell of Kulchitsky in the submucosal layer. Their size are around few centimeters. Metastasis in liver, omentum and peritoneum. In case of sarcoma, the best histologic criterion of malignancy is based on the presence of mitotic activity, cellularity and pleomorphism. They have predominance of vascular embolization. Those adenocarcinoma tumors have poor prognosis with metastasis to lymph nodes and liver. Diferent types of described adenocarcinoma arose of the small bowel and gastric mucosa. (see Table 2).

TABLE 2
TUMOR CLASSIFICATION
IN MECKEL'S DIVERTICULUM[11-14]

A- BENING TUMORS:
1. CONECTIVE TISSUE
2. SMOOTH MUSCLE
3. VASCULAR TISSUE
4. FATTY TISSUE
5. NERVOUS TISSUE

B- MALIGNANT TUMORS:
1. CARCINOID TUMOR
2. ADENOCARCINOMA
3. SARCOMA

Resumen: *El divertículo de Meckel es un vestigio del conducto onfalomesentérico debido a un defecto de su reabsorcion. El caso a presentar se caracteriza por presentar*

las características menos comunes de este tipo de malformación. La presencia de obstrucción intestinal, anemia sintomática sin presencia de sangrado evidente, el tamaño desmesurable del divertículo como la presencia de un leiomioma hacen de este caso algo infrecuente. Se describen en este artículo el conjunto de manifestaciones poco usuales de esta malformación y su completa recuperacion luego de cirugía.

References:

1. Robert P. Foglia: Meckel's Diverticulum. Pediatric Surgery Textbook. Ashcraft and Holder.W.B. Saunders. 2ed. : 435-39, 1993.

2. Jay GD, Margulis RR, McGraw AR et al. Meckel's Diverticulum: A survey of 109 cases. Arch Surg. 61:158-69, 1950.

3. Soltero JH, Bill A: The natural history of Meckel's Diverticulum and its relation to incidental removal. Am J Surg 32:168-173, 1976.

4. Miller DL, Becker MH, Eng K: Giant Mekel's Diverticulum: A cause of intestinal obstruction. Radiology 140:93-94, 1981.

5. Mackey WC, Dineen P: A fifty year experience with Meckel's Diverticulum. Surgery, Gynecology & Obstetrics. vol 156, January 1983.

6. Torii Y, Hisatsune I, Imamura K, et al: Giant Meckel's Diverticulum containing enteroliths diagnosed by computed tomography and sonography. Gastrointest Radiol 14:167-69,1989.

7. Yates HB: A remarkable Meckel's Diverticulum. Br J Surg 17:456-462, 1930.

8. LouW JH: Embryology and development anomalies of the small and large intestines. Part I In: Bockus HL (ed): Gastroenterology 3rd. edition, vol.2. W.B. Saunders,1976.

9. Rutherford RB and Akers DR: Meckel's Diverticulum: a review of 148 paediatric patients, with special reference to the pattern of bleeding and to mesodiverticular bands. Surgery 59:618-26, 1966.

10. Curd HH. A histologic study of Meckel's Diverticulum with special reference to heterotopic tissues. Arch Surg 32:506, 1936.

11. Weinstein EC, Dockerty MB, Waugh JM: Neoplasms of Meckel's Diverticulum. International Abstracts of Surgery Vol. 116, Feb. 1963.

12. Dockerty MB, Ashburn FS: Carcinoid tumors of the ileum: report of 13 cases of metastasis. Arc Surg 47:221, 1943.

13. Fahim RB, Pratt JH: Leiomyosarcoma of Meckel's Diverticulum. Minessota M 42:1269, 1959.

14. Costich KJ, McNamara WL: Carcinoma of Meckel's Diverticulum: case report. Ann Surg 124:503,1946.

- La determinación es la fuerza que tiene el poder de limpiar nuestro corazón de toda traza de olvido, ignorancia o pereza.

Abad Marcos

Reporte de Caso:

What is your diagnosis

First Author: José R. Rivera Del Río, MD*;
Co-Authors: Juan R. Vilaró, MD; Juan Igartúa, MD

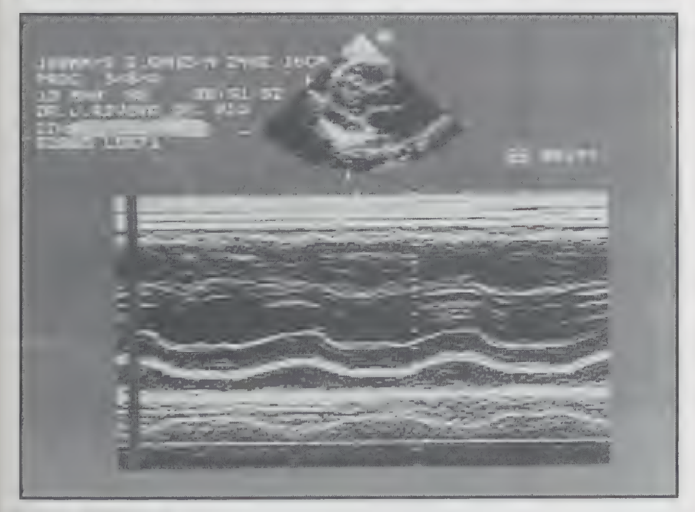
Mr. HPV is 28 years old male patient who since 4 months ago started with decreased appetite, tiredness, cough and dyspnea on exertion. There was no past history of importance and no recent pertinent illness. Distended jugular veins, non specific EKG findings and increased heart size by chest x ray were reported. An echocardiography only detected a large pericardial effusion with normal ejection fraction and he was admitted to the hospital where a complete work up and more thorough physical examination was done. He was found with 10 cm JVD, no pericardial friction rub, no Kussmaul sign and no paradoxic pulse. No other significant finding could be detected. Laboratories: Sed rate, ANA, RA, PPD, CBC, SMA 20, TSH, U/A, Echovirus, Mycoplasma, and Coxsackievirus titers all were normal. The patient was discharged home with indometacin therapy and close follow up was made. The first follow up visit was characterized by a mild improvement in symptoms. After 2 months the patient started to notice decreased appetite, distended abdomen, leg edema, dyspnea on exertion and more neck vein distention. The physical examination now presented a 12 cm JVD with positive Kussmaul sign, positive hepatojugular sign, a friction rub, a rapidly collapsing *y* descent, hepatomegaly, leg edema and 10 mmhg paradoxic pulse determination. The next echo views were done at that moment.



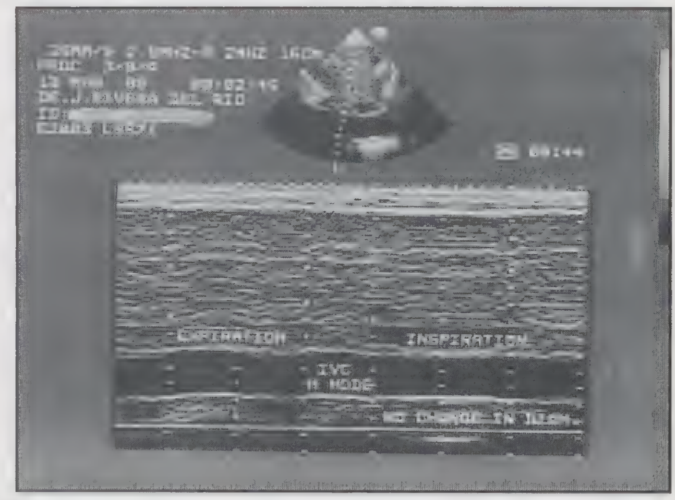
ECHO VIEW # 1



ECHO VIEW # 3



ECHO VIEW # 2



ECHO VIEW # 4

* Cardiology Division Director, Internal Med. Dept.; Universidad Central del Caribe - Call Box 60-327, Bayamón, PR 00960-6032

What is your diagnosis:
1. **Pericardial tamponade**
2. **Chronic constrictive pericarditis**
3. **Restrictive cardiac disease**
4. **Effusive constrictive pericarditis**

The diagnosis is # 4.

This patient had another laboratory evaluation which again failed to demonstrate a specific etiology for the present condition. A chest CT and abdomen CT were done which confirmed the cardiac pathological echo findings, detected hiliar nodes, and reported a passive abdominal organs distention with tense ascitis. No calcification in the pericardium was reported.

The progression and change in physical examination in this patient characterizes the diagnosis. It can be considered as a sub acute form of pericardial inflammation process in its passage to chronic constriction. The usual absence of a positive paradoxic pulse is described in this entity in view of the predominant constrictive pathophysiology. The Kussmaul sign (Lack of fall, or even increase, of the systemic venous and right atrial pressures during inspiration) is the consequence of the failure of intra thoracic pressure changes during respiration to be transmitted to the pericardial space and intra cardiac chambers. The clinical findings are partly the result of the imposed restriction to diastolic filling which results in compensatory renal retention of sodium and water (and inhibition of the atrial natriuretic factor?) that contributes further to the increase in systemic pressure which initially serves to maintain diastolic filling of the ventricles. The rest of the symptoms were explained by the reduced cardiac output. The rapid ***y*** descent is present in this constrictive state and represents the ability of the right ventricle to fill fast in early diastole with an increased venous pressure.

The EKG was non diagnostic as usually seen in this condition. The echocardiogram in this case allowed a clear definition of the patient pathology. The first view is a parasternal long axis at diastole which depicts a thickened pericardia with moderate effusion. It is important to acknowledge the fact that the rest of the bidimensional echo failed to present any other abnormality misdirecting the diagnosis. The M mode (ECHO VIEW # 2) presented an early posterior inter ventricular septum movement and a "flat" posterior endocardial movement at late diastole both characteristic of the constrictive effect. The third and fourth echo view shows a markedly dilated inferior vena cava with no changes in the respiratory cycle exemplifying the increased systemic venous pressures. The Doppler was also done in this patient and presented a high E velocity classically due to the abnormally rapid early diastolic filling associated with the combination of a small volume and rapidly recoiling ventricle.

In view of the lack of other plausible explanation for the patient findings (Lung diseases, right side valvular pathology, restrictive cardiac disease, abdominal pathology, etc.) with active constrictive clinical features and with the presence of hiliar nodes; a need for diagnosis and surgical correction was decided before any other medical therapy was attempted. The intra cardiac hemodynamic measurements was not considered to add more differential diagnostic information and the coronary status was not an issue in this case. The patient underwent phrenic to phrenic pericardiectomy with decortication of cardiac peel. A one centimeter thick pericardium specially involving the right ventricle was found. The pathological findings were reported as a chronic inflammatory pericardia with fibrosis and the hiliar nodes had follicular hyperplasia. No specific pathogen or malignancy was identified. These findings are consistent with the 42% unknown etiology (Sometimes attributed to not detected viral process) described in this condition. The patient is recuperating fast and the postoperative physical evaluation presents decreased systemic pressures (No JVD and less ascitis), improved appetite and no dyspnea on exertion.

References:

1. Chafizadeh, E,Shabetai, R. (1997) Pericardial Compressive Syndromes. "UpToDate". Vol.6 No.1.
2. Lorell, EH. Pericardial Diseases. Chapter 43. Braunwald; Heart Diseases, 5th Edition. Saunders 1997. pp1478-1535

- Quien no tiene nada que ofrecer, tampoco recibe nada.

Kurt Heine

Vol. 90 • 1 - 2 - 3 / 1998 • Pág. 42, 44

Artículos Especiales:

Pacientes regulados como modalidad de evaluación en la ejecutoria clínica

Marta Febo López, MD, ABDFP
Directora Programa Pacientes Regulados - Escuela de Medicina de Ponce

Abstracto: La incorporación de pacientes regulados en la enseñanza clínica de estudiantes de medicina comenzó su desarrollo en Estados Unidos para los años 60. Al presente muchas escuelas de medicina utilizan pacientes regulados en diversas actividades de enseñanza. De esta manera se ha podido desarrollar una experiencia de aprendizaje y/o evaluación homogénea para todos los estudiantes expuestos a la misma. En la actualidad se ha comenzado a extender la utilización de pacientes regulados a la sesión clínica de los exámenes necesarios para obtener licencia médica en lugares como Canadá. Próximamente se incorporarán pacientes regulados a la parte clínica del USMLE. A través de este artículo pretendemos compartir en alguna medida la experiencia de la Escuela de Medicina de Ponce y su Programa de Pacientes Regulados. Al presente esta institución académica entra en su tercer año de experiencia y desarrollo de esta modalidad de enseñanza clínica. La incorporación de pacientes regulados en el proceso de enseñanza clínica en la Escuela de Medicina de Ponce incluye: experiencias básicas en la toma de historial, examen físico y destrezas de entrevista para estudiantes en cursos introductorios a la medicina clínica en 2do. año, experiencias para establecer necesidades y expectativas del estudiante en tercer año, así como sesiones formativas durante la pasantía de tercer año en todas las rotaciones clínicas. La experiencia de un examen clínico práctico se ha estado trabajando para incorporarse el próximo año académico. El futuro y la aportación en la investigación educativa que pueda tener esta modalidad se encuentra en pleno proceso de desarrollo. Por lo pronto la modalidad de pacientes regulados ha logrado llenar una necesidad en la enseñanza clínica que valida de manera sólida su utilidad.

En la actualidad un número significativo de Instituciones a cargo de la formación clínica de los estudiantes de medicina continúan trabajando para desarrollar estrategias de evaluación clínica para los estudiantes.

En la enseñanza clínica, las preocupaciones de los educadores han sido consistentes. Es importante la observación directa al estudiante en su trabajo clínico, se necesitan casos representativos donde se puedan observar destrezas clínicas específicas y es necesario además garantizar experiencias clínicas similares que puedan repetirse a lo largo de la formación clínica de los estudiantes.

De no satisfacer las necesidades antes mencionadas, ¿puede una institución decir que sus estudiantes tienen las destrezas necesarias para continuar su desarrollo clínico?

Hasta la década de los 60 la respuesta era No. Sólo en algunos casos el educador clínico podía con alguna certeza garantizar que algún estudiante en particular había desarrollado las destrezas clínicas necesarias para su etapa de adiestramiento.

Para el 1964, en Estados Unidos Barrows y Abrahamson proponen la utilización de pacientes regulados ("Standardized Patients") en la enseñanza clínica. (Barrows & Abrahamson, 1964; Barrows 1987).

Se define como paciente regulado ("Standardized Patient") a una persona saludable o estable en su condición de salud que es adiestrada para representar un cuadro clínico específico. Esta persona se adiestra en los elementos del historial, examen físico o intervención de manejo y consejería para el caso que esté representando. Su adiestramiento incluye además aspectos de la entrevista médica o elementos en la relación médico - paciente para establecer empatía y como ofrecer "feedback" al estudiante luego del encuentro médico - paciente. A lo largo de su preparación como paciente regulado la persona adiestrada continua desarrollando las destrezas que le permiten convertirse en un asistente para la enseñanza clínica del estudiante de medicina.

Desde los comienzos, la utilización de esta modalidad varía desde una experiencia formativa integrada a la enseñanza clínica, hasta una requerida para evaluación al finalizar el tercer ano o comenzar el cuarto año de medicina. En una encuesta realizada en 1989, en Estados Unidos y Canadá de 142 escuelas de medicina incluidas en la encuesta respondieron 136. De estas 94 (70%) indicaron la utilización de pacientes regulados en diferentes actividades de enseñanza clínica. (Academic Medicine, 1993; Vol. 68, 6, (454-460).

La utilización de pacientes regulados se ha expandido fuera de las escuelas de medicina. En Canadá por ejemplo a partir de 1993, se comenzó a utilizar

pacientes regulados en el examen requerido para obtener la licencia que permite la práctica de la medicina en ese país. La Junta Nacional de Exámenes de Medicina ("National Boards of Medical Examiners") en Estados Unidos aprobó recientemente la utilización de pacientes regulados en el USMLE II. Se espera que la evaluación clínica de los participantes en el USMLE, comience a incorporar pacientes regulados en su segunda parte para los años 1999-2002.

En la Escuela de Medicina de Ponce, para el 1995, el Departamento de Medicina de Familia estableció una Unidad de Pacientes Regulados utilizando fondos asignados por el Instituto Nacional através de una propuesta sometida con este propósito.

Para enero de 1997 en esta institución se comenzó a expandir la utilización de pacientes regulados en todos los departamentos clínicos y al curso de Introducción a la Medicina Clínica Durante el año académico 98-99 se comenzará a ofrecer un examen clínico formativo utilizando pacientes regulados para los estudiantes que comienzan su cuarto año.

A continuación un ejemplo de 7 casos que pueden ser incluidos en un examen clínico, y cuales son las destrezas que pueden ser evaluadas con cada uno de los casos. Algunos de los encuentros con pacientes regulados anteceden lo que se conoce como una estación post-encuentro. En dicha estación el estudiante podrá contestar preguntas relacionadas al caso, evaluar laboratorios y/o estudios radiológicos entre otras. Entre otras destrezas clínicas que pueden evaluarse en la estación post-encuentro se encuentran: diagnóstico diferencial y manejo clínico del caso. (Ver tabla 1 y 2)

Luego de 2 1/2 años de utilizar pacientes regulados en la enseñanza clínica podemos resaltar los beneficios de esta modalidad así como sus debilidades. Definitivamente nos parece que estamos ante la experiencia clínica más cercana a la realidad de evaluar y manejar a los seres humanos que solicitan servicios médicos. Además, esta estrategia ofrece la posibilidad de observar a los estudiantes de medicina utilizando experiencias clínicas similares, donde el educador determina de antemano las destrezas que se van a evaluar. La

Tabla 1.
Ponce School of Medicine

STANDARIZED PATIENT PROGRAM

PATIENT PROBLEM	SKILL REQUIRED									POST ENCOUNTER AVAILABLE					
	HX TAKEN	PH TAKEN	INTER-PERSONAL SKILLS	DATA INTERPRE-TATION	PROBLEM SOLVING	HRA/HM	PATIENT EDUCA-TION	PROCEDURE	PATIENT SATIS-FACTION	CONF HX	CONF P E	DIF DX	DIAG PLAN	THERAP PLAN	RECORD KEEPING
ACUTE ABDOMINAL PAIN (RUQ)	1	1		1	1										
SECONDARY AMENORRHEA -IUP -THREATENED ABSORTION	1	1		1	1		1								
MAYOR DEPRESSION COMPLICATED	2	1	1	2	1		1	1							

LECTURE (3) COMPREHENSIVE (2) ORIENTED TO PATIENT PROBLEM (1) FOCUS ON PATIENTS COMPLAIN

Tabla 2.
Ponce School of Medicine

STANDARIZED PATIENT PROGRAM

PATIENT PROBLEM	SKILL REQUIRED									POST ENCOUNTER AVAILABLE					
	HX TAKEN	PH TAKEN	INTER-PERSONAL SKILLS	DATA INTERPRE-TATION	PROBLEM SOLVING	HRA/HM	PATIENT EDUCA-TION	PROCEDURE	PATIENT SATIS-FACTION	CONF HX	CONF P E	DIF DX	DIAG PLAN	THERAP PLAN	RECORD KEEPING
ADOLESCENT WITH HEADACHE -DIS DX DEATH ISSUES	2	2	1	1	1		2								
URTI-PED DEPT MALE TO R/O ABUSE	1	1	3		1	1	2								
HEADACHE ADUTL FEMALE NEUROLOGIC EXAM	2	2		1	1		1								
CHEST PAIN MALE -ANGINA -CV RISKS	1	1		1	1										
BREAST MASS -BENIGN -BREAST EXAM	1	1		1	1		1								

LECTURE (3) COMPREHENSIVE (2) ORIENTED TO PATIENT PROBLEM (1) FOCUS ON PATIENTS COMPLAIN

experiencia puede repetirse cuantas veces sea necesario para observar diferentes estudiantes o dar seguimiento a observaciones hechas previamente a algún estudiante en particular. Esta modalidad de enseñanza ha resultado ser muy buena para utilizarse en grupos pequeños así como demostraciones en grupos grandes, especialmente en cursos introductorios a la medicina clínica.

Hasta el presente la opinión de los estudiantes ha sido consistente: Los talleres donde se utiliza pacientes regulados es una experiencia de gran valor y utilidad donde pueden aprender en un ambiente controlado en el cual se puede cometer errores sin que se perjudique el estudiante y/o el paciente.

Hemos podido reconocer que la enseñanza clínica utilizando pacientes regulados puede convertirse en un reto tanto para el estudiante como para el educador. Aparenta ser una modalidad de enseñanza que puede generar un alto nivel de tensión para todos, pero más aún para personas sensitivas a ser observadas, grabadas y/o evaluadas. Se convierte así en parte de las tareas del educador el aprender a identificar y manejar estas situaciones. El proceso de retroinsumo que se genera en las sesiones con pacientes regulados puede convertirse en una fuente adicional de estrés. Nuevamente el facilitador es responsable de conocer y facilitar un proceso de "feedback" para que se convierta en una experiencia de aprendizaje para todos los participantes. Por otro lado, el proceso de discusión que se produce usualmente en las sesiones de grupo ofrece una oportunidad al estudiante para cuestionar al educador, convirtiéndose así cada sesión en una experiencia educativa única y retante para el facilitador.

En nuestra experiencia hemos encontrado que con una supervisión adecuada, la labor del paciente regulado se mantiene consistente en realismo y dominio de su representación. Su capacidad discriminatoria, de observación y capacidad para ofrecer retro-insumo puede desarrollarse a un nivel donde se convierten en verdaderos asistentes en la enseñanza clínica. En los estudios realizados para evaluar la consistencia y precisión de los pacientes regulados se evalua como excelente si mantienen consistente su representación y la información que le proveen al entrevistador. Además si el reporte de destrezas observadas revela más de un 80% de concordancia al compararlo con un reporte igual completado por un observador cualificado se clasifica como excelente la tarea del paciente regulado (Ac. Med. 1993 Vol. 68, 6, 454-460). En el Programa de Pacientes Regulados de la Escuela de Medicina de Ponce, el adiestrador de los pacientes mantiene una supervisión constante para observar la representación y periódicamente completa la lista de cotejo para el caso y evalúa el porciento de concordancia entre ambos. Al presente el mismo se ha mantenido sobre 80% en todos los casos. De surgir un resultado menor de un 80%, el caso se revisaría para re-adiestramiento en completar la lista de cotejo.

Existen otras áreas en la formación profesional del médico que tradicionalmente no se podían evaluar en la mayoría de los estudiantes en donde la utilización de pacientes regulados adquiere un valor excepcional. Con esta modalidad un educador puede reconocer si el estudiante además de conocimiento posee las destrezas de comunicación necesarias para establecer una relación médico-paciente efectiva. Puede además observar si el comportamiento profesional del estudiante es apropiado o no y ofrece la valiosa oportunidad de obtener retroinsumo del paciente sobre su grado de satisfacción con la intervención del estudiante.

Sin embargo, es necesario señalar que utilizar pacientes regulados en la enseñanza clínica puede resultar una modalidad costosa, y que requiere inicialmente una inversión económica y de esfuerzo humano significativos. En nuestra experiencia podemos señalar que la aportación educativa que se incorpora a la formación clínica del estudiante de medicina justifica la inversión y sobre todo su utilización.

El futuro de esta estrategia continúa en desarrollo para el beneficio de la educación médica. Ya se definen como instructores aquellos pacientes regulados que desarrollan destrezas para dar retroinsumo al estudiante y aquellos que asisten al estudiante en el desarrollo de destrezas de examen físico. Además, esta estrategia nos ofrece información suficiente para realizar investigación educativa. Y aunque incorporarla a la enseñanza clínica requiera de tiempo; adiestramiento y mucho trabajo tanto el estudiante como el educador disfrutaran de la oportunidad de aprendizaje que ofrece esta modalidad.

Referencias:

1. MB Anderson, P.L. Stillman and Youde Wang; Growing Use of Standardized Patients in Teaching and Evaluation in Medical Education. Clinical Learning in Medicine Vol. No. 1, 15-22.

2. R.M. Harden and F. A. Gleeson Assessment of Clinical Competence Using and Objective Structured Clinical Examination (OSCE) 1979, 13, 41-54

3. N.V. V.U. M. Marcy, J.A. Colliver, S. J. Velhulst, T.A. Travis and H. Barrows; Standardized Patient Accuracy in Recording Clinical Performance Check list Items, Medical Education 1992, 26, 99-104.

4. Tamblyn R. M., Klass D. J. Schakl G. K. and Koplin M. L.; The Accuracy of SP Presentation. Med. Educ. 25 (1991): 100-109.

 Vol. 90 • 1 - 2 - 3 / 1998 • Pág. 45, 50

Artículos Especiales:

The development of a course in basic physical examination skills

Luisa I. Alvarado, MD, FAAP
Associate Professor, Chairperson Department of Pediatrics, Ponce School of Medicine, Ponce, Puerto Rico

Abstract: Basic clinical skills of most medical school undergraduates continue unobserved and deficiencies have been detected in a significant number of physicians during residency. Nevertheless, our health care system is calling for competent graduates with solid basic clinical skills and a larger representation of qualified generalists in the increasingly important managed care environment.

The need for a better Introduction to Clinical Skills course was identified by students and clinical faculty at Ponce School of Medicine. In response to these concerns a new curriculum was developed with clear objectives, effective instructional strategies, and performance-based evaluation, with adult learning principles as its framework. The musculoskeletal examination unit of the curriculum was pilot tested and the course evaluation strategies revealed satisfaction with objectives, instructional and evaluation strategies, as well as improved confidence, and sense of usefulness for the learned skills.

A curriculum in basic clinical skills that incorporates adult learning principles with solid instructional strategies can increase the confidence and skills of the learners and should lead to improved outcomes.

History-taking and physical examination skills are the cornerstone of the medical education process, because they are the principal means of collecting clinical data to develop the evaluation and problem solving skills needed for optimal patient care. Effective clinical skills are the clinicians' most important investigative tools in the scientific approach to the patient's problem.[1] Medical school graduates need the skills to acquire clinical data by history-taking and physical examination, as well as the interpersonal qualities and attitudes that promote effective doctor-patient relationships. Assuring that instruction and evaluation is consistent with this mission, continues to be a challenge for US Medical Schools[2]. In spite of its critical importance in the development process of future physicians, clinical skills courses continue to have problems of effectiveness and consistency in teaching and evaluation. In fact, a large proportion of medical students continue to graduate without ever been observed performing a history and physical examination[3], and studies reveal that basic history-taking and physical examination skills may be deficient in a significant number of residents in postgraduate training.[4,5] In 1990 the Association of American Medical Colleges (AAMC) acknowledged these challenges by establishing a Special Interest Group on Introduction to Clinical Medicine to continue discussing the development and improvement of early clinical skills. In 1989 several key North American organizations, including the American Board of Medical Specialties (ABMS), the American Medical Association (AMA), the Association of American Medical Colleges (AAMC), the National Board of Medical Examiners (NBME), the Medical Council of Canada (MCC), and others, established the Clinical Skills Assessment Alliance (CSAA) with the intention of promoting clinical skills competence and performance evaluation strategies.[6] The CSAA works through its member organizations to assure that medical students' clinical performance is evaluated by direct observational methods, of which standardized patients have evolved the most valid and reliable, but the most expensive.

Since managed care organizations are becoming an increasingly important element in the delivery and financing of health care in the nation, we as educators need to assure that medical school graduates have effective and efficient clinical skills to practice in a system that emphasizes cost effective health care.[7] Solid communication and physical examination skills are essential for a competent and efficient medical practice, and we need to continue reforming our teaching and developing curricula to address this need.

The fact that faculty role models can influence medical students' attitudes toward the different medical specialties, poses another challenge to clinical skills courses. While health policy experts believe that generalists should constitute about 50% of all physicians in practice, currently no more than 30% of the nation's practitioners are generalists.[8] The AAMC in its Policy on the Generalist Physician of October 1992, states that medical schools can infiuence specialty choice by exposing medical students to generalists physicians early in their educational careers.[9] Generalists as teachers and positive role models in introductory clinical skills courses could have significant

impact on physician resources by stimulating students choice of generalist careers.

At Ponce School of Medicine in Puerto Rico, dissatisfaction with the course on basic physical examination skills for second-year medical students had been expressed by clinical faculty and medical students. The need for clear objectives, the inconsistent instructional activities and evaluation processes, and problems with variable skills of the teaching faculty were the main concerns identified. To address these issues a new curriculum was developed incorporating effective, consistent instructional strategies, performance-based evaluation, and a generalist faculty. This paper provides a detailed description of this curriculum, the development process, and the implementation of a unit as a pilot test.

Development Process

A thorough needs assessment was conducted motivated by Ponce School of Medicine student and clinical faculty concerns. The top 10% of graduates of the second year course were interviewed about their experiences, skills, and confidence after the course.

This information was complemented with a Clerkship Directors Survey (n=6) and other informal communications. The information obtained confirmed the problems previously suggested. Of special concern was finding of poor confidence levels among top of the class students and the absence of pediatric physical examination skills in the students interviewed.

In preparation for the development of a new curriculum, an extensive MEDLINE search of medical education literature was performed. Articles addressing different instructional strategies, teaching resources, and evaluation processes were included in the needs assessment. Basic clinical skills curricula have received significant attention in the medical education literature producing information of extraordinary usefulness to curriculum developers. The literature describes strategies to address consistency of teaching, faculty availability and faculty skills, among others. Structured courses, development of senior students as teachers, and utilization of student developed instructional materials have been successful at some institutions.[10,11,12,13] According to Solomon, et al. a developmental approach to physical examination was effective for teaching pediatric and geriatric physical examination at Michigan State University.[14] Confidence in psychomotor skills can be improved by repetition and practice opportunities as emphasized in an article by Klachko, et al. from Missouri-Colombia Medical School.[15]

The usefulness of standardized patients in assuring consistency in the teaching of clinical skills and overcoming faculty availability problems is addressed in several articles.[16,17] Validity and reliability of standardized patient student evaluation is discussed in the above and other articles.[18,19,20] We were able to review examples of an advanced physical examination course to supplement senior medical students' skills,[21] and a student-centered active approach to clinical skills teaching.[22] As our developmental framework we have used the following adult learning principles construed from the continued medical education literature:[23]

- "Emphasis on the entire learning environment"- A supportive environment will guarantee active student participation and opportunities for feedback.

- "Emphasis in the context in which learning occurs"- Learning experiences in the real life context in which the student will practice will be remembered better, and recalled for future patient problems.

- "Learning around clinical problems"- Provides the store of clinical data from which knowledge and skills can be retrieved.

- "Use of the group"- The opportunities for discussion and feedback are enhanced, as well as exposure to role models, learning from peers, enjoyment and support.

- "Enhancing self efficacy"- Hands on practice will develop confidence and ability to perform.

- "Building needed skills"- Acquisition of self learning skills by deciding own learning needs and developing the skills to fulfill them.

These articles provided valuable ideas and guidance for the development of a new clinical skills curricula in our medical school. Additional information obtained from the 1995 National Meeting of the AAMC and personal communication with basic clinical skills experts was incorporated. Also useful to the development process was the access to other medical school curricula. Examples of Introduction to Clinical Skills Curricula from the University of Puerto Rico (UPR) School of Medicine, Boston University (BU) School of Medicine, and Michigan State University (MSU) College of Human Medicine were reviewed. The idea of alternating experiences in adult and pediatric physical examination at UPR; the developmental approach to physical examination in Pediatrics at BU, and the use of small groups for practice with peers and patients at MSU, were incorporated in our design. I am grateful to these institutions for allowing me to review their curricula.

In the development of our curriculum, ten instructional units were chosen to represent the steps

necessary to perform a comprehensive physical examination (Table I). Two additional units emphasize the integration of all skills in an adult and a pediatric patient. Physical examination checklists for each instructional unit and a comprehensive final checklist were carefully constructed to include detailed descriptions of the desired skills. The references used to construct our checklists were, the Standard Physical Examination Checklist from the Special Interest Group (SIG) in Introduction to Clinical Medicine of the AAMC, and the work of Dr. Paula L. Stillman and Ms. Gayle Gliva. These checklists are intended to guide faculty demonstrations, student practice, and the evaluation process.

Table 1.
Instructional Units

Instructional Unit	Duration % Course Time
1. Approach the patient, assess his or her general and emotional status, obtain vital signs	5.5 hours - 7%
2. Examination of the head, eyes, ears, nose, throat and neck	9.5 hours - 12%
3. Examination of the thorax and lungs	5.5 hours - 7%
4. Examination of the cardiovascular system	11.0 hours - 13%
5. Examination of the abdomen	5.5 hours - 7%
6. Musculoskeletal examination	5.5 hours - 7%
7. Examination of the skin	1.5 hour - 2%
8. Female genitalia and breast examination	4.0 hours - 5%
9. Examination of the male genitalia	1.5 hours - 2%
10. Neurologic examination	9.5 hours - 12%
11. Integration of complete adult examination	7.0 hours - 9%
12. Examination of the pediatric patient	16.5 hours - 20%

Prior to implementation, a final evaluation of the curriculum content and process was accomplished by the review of nationally recognized experts. Dr. Benjamin S. Siegel, Director of Medical Student Education in Pediatrics at Boston University School of Medicine, and collaborator in the General Pediatric Clerkship Curriculum developed by the Council of Medical Student Education in Pediatrics (COMSEP) and the Ambulatory Pediatric Association (APA), and Dr. Mary Ann Antonelli, Moderator of the Special Interest Group in Introduction to Clinical Medicine of the AAMC, and Director of the Clinical Skills Course at West Virginia School of Medicine, analyzed the content and provided the developer with excellent recommendations. A pilot test of one of the instructional units was designed as part of the curriculum development process. This paper presents the pilot test and a discussion of its results, which can be useful to other clinical skills curriculum developers and faculty.

The Curriculum

The primary goal of our curriculum is to teach the skills of a comprehensive physical examination to second-year students in order for them to perform efficiently, effectively, and with confidence. The course will capacitate students to understand the anatomic, physiologic and pathophysiologic principles involved in the examination, and to develop the sensitive, respectful and professional attitudes that should be exhibited at all times in the interaction with patients.

A series of instructional units (Table I) display the logical sequence of the examination that students will learn and continue using. Each instructional unit contains the content, instructional and evaluation strategies required to teach and evaluate every component of the physical examination. Table II presents the example unit on the musculoskeletal examination. This example represents the template by which most units will be developed.

Instructional strategies consist of an assigned reading, a lecture enhanced with audiovisual and/or demonstration, and a clinical practice with peers and patients. After the lecture, clinical preceptors demonstrate the skill by using the unit checklist as a guideline, reducing the variability from individual skills, styles, and preferences. The student then uses the checklist as reference during the practice with peer session. An additional practice with patient session is meant to develop confidence by repeating the routine in a real world setting. Students practice in pairs taking turns as performers or recorders of the checklist. Feedback is provided by peers and the preceptor in a non threatening, formative context.

All units include practice with peers and patients, except for female and male genitourinary systems. The final units were designed to deal with integration of the adult and pediatric physical examination skills and follow the same instructional strategies. This curriculum has been designed so that standardized patients can be introduced for teaching and evaluation, anticipating their inclusion in our institution. Effectiveness of the curriculum will be

Table II.
INSTRUCTIONAL UNIT 6
Musculoskeletal Examination

Unit Goal: The student will efficiently and effectively examine the musculoskeletal system including upper extremities, lower extremities, neck and spine, using the inspection and palpation techniques that are indicated for each part of the examination, while exhibiting a sensitive, respectful, and professional attitude.

Unit Learning Objectives	Unit Content	Unit Instructional Strategies	Unit Learner Evaluation Methods
1. Given a series of cases in a written test, the student will recognize the anatomic, physiologic, and pathophysiologic principles related to the examination of the musculoskeletal system with at least 70% accuracy.	1. Anatomy and Physiology of the: Upper extremities Lower extremities Spine Structure and function of joints 2. Abnormal findings	1. Assigned Reading: *Barbara Bates, The Musculoskeletal System: Anatomy and Physiology, Chapter 17, p. 449-463.* 2. Lecture with *A Visual Guide to PE- Musculoskeletal examination.*	1. Written examination with MCQs.
2. Given a genuine or standardized adult patient, the student will examine the upper and lower extremities, neck, and spine. according to a checklist, and with at least 90% completion with competency.	Examination techniques: 1. Hands and wrists: inspection, palpation, range of motion (ROM) 2. Elbows: inspection, palpation, ROM 3. Shoulders: inspection, palpation, ROM 4. Hips and Knees: inspection, palpation, ROM 5. Ankles and feet: inspection, palpation, ROM 6. Neck: inspection, palpation, ROM 7. Spine: inspection, palpation, ROM	1. Assigned Reading: *Barbara Bates, The Musculoskeletal System: Techniques of Examination, Chapter 17, p. 464 - 480.* 2. I.ecture *with A Visual Guide to PE* Audiovisual. 3. Preceptor demonstration (30 min) and practice with peers using PE **Checklist** (1.5 hr). 4. Practice with patients using PE **Checklist** (1.5 hr).	1. Peer observed physical examination on patient using **Unit PE Checklist** 2. Evaluation and feedback by clinical preceptor and peer using **Unit PE Checklist** results (30 min). (Formative) 3. Faculty observed physical examination using **Comprehensive PE Checklist.** (Summative Final)
3. Given a genuine or standardized adult patient, the student will examine the musculoskeletal system while behaving in a sensitive, respectful, and professional manner, according to a checklist, with al least 90% completion with competency.	1. Informed consent 2. Sensitivity to patient needs, comfort and concerns 3. Avoid excessive discomfort or pain 4. Position and draping techniques	1. Lecture 2. Clinical preceptor demonstration	1. Peer observed physical examination on patient using **Unit PE Checklist.** 2. Evaluation and feedback by clinical preceptor and peer using **Unit PE Checklist** results. (Formative) 2. Faculty Observed physical examinlation using **Comprehensive PE Checklist** (Summative - Final).

established by a final faculty-observed physical examination using the comprehensive checklist. This performance-based evaluation guarantees that the student possesses the skills expected for his level and to progress in the educational process. Written examinations will be used to evaluate student understanding and knowledge of the material. Course evaluation by student and faculty will take place after each unit and provide information for continued improvement.

Results

A pilot test of the musculoskeletal examination unit was conducted with the participation of the current group of second-year students, a lecturer from the Department of Internal Medicine, and the actual clinical preceptors, Internal Medicine faculty and senior residents. Before the pilot, meetings were held with faculty and students to present objectives, instructional strategies and checklists. Materials for

individual reading were assigned one week prior to the pilot. Faculty was also introduced to the video and the checklist, one week prior to the activity. The students were given an introductory lecture enhanced with an audiovisual presentation of the musculoskeletal examination. After the lecture, the large group observed a faculty demonstration of the skills and went into small groups for the practice with peers. Students and small group preceptor used the musculoskeletal checklist as a guide for the practice session. An enthusiastic reaction to the pilot was observed by the curriculum developer during this introductory phase.

Lecture, video and demonstration were given within the scheduled time, with positive reactions observed from the learners, as noted by attendance and active participation. Clinical practice took place in the hospital setting with the previously assigned clinical preceptors. At the end of the activity, the students that participated in all components (n=45) were asked to rate their satisfaction level using an opinion survey graded with a five point Likert scale.

Opinions were graded between l = relates to very little to the assertion, and 5 = relates to very much to the assertion. The students' mean ratings to each positive assertion about the curriculum components are shown in Table III. These results show that the learners were satisfied with the unit in most of the parameters examined. Students' mean response to: "After the experience, I feel confident in performing the musculoskeletal examination" was 4.4. The mean response to: "I will continue using this sequence of examination" was 4.4, and to: "I enjoyed the educational experience" was 4.8. Most students (80%) answered either 4 or 5 for level of confidence at the end of the experience.

Discussion

A curriculum to teach basic skills of a comprehensive physical examination to second-year students, and the evaluation of its pilot test have been presented. We developed well defined objectives, matched them with effective instructional and evaluation strategies, to produce a consistent educational experience which was enjoyable and effective. The use of small groups, practice in real-life context, timely feedback, and a supportive educational environment facilitated and supported adult learning. The results of the pilot test support increased confidence and enjoyment in our learners.

From the pilot test we learned that faculty development is essential to the success of the activity. In preparation for full implementation, this aspect needs careful and decisive attention. Qualified generalist faculty needs to be identified and recruited, and intensive, periodic faculty development activities need to be offered.

Our learners expressed confidence in their recently acquired skills and based on the report of graduates of the previous course, we believe we accomplished higher confidence levels, enjoyment, and a better appreciation of the usefulness of the learned skill. Performance based evaluations will further document the effectiveness of the curriculum. This will be accomplished by faculty-observed physical exami-

Table III.
Pilot test of musculoskeletal unit satisfaction ratings

Category	Mean Response	Standard Deviation
1. The learning objectives were clear.	4.0	0.9
2. Learning activities gave me an adequate opportunity to master the objectives.	4.1	0.7
3. Material in the lecture closely related to the stated objectives.	4.1	0.7
4. Lecture was understandable, interesting, and cpmplete.	3.8	0.9
5. Audiovisual presentation was useful.	4.3	0.7
6. Activities with preceptor closely matched the objectives.	4.2	0.7
7. Practice with peers was useful to master the skill.	4.3	0.7
8. Practice with patients was useful to master the skill.	4.3	0.6
9. Feedback was provided in a positive, constructive way.	4.1	0.7
10. The Checklist was useful to evaluate my skills.	4.3	0.7

nations, and in the future by standardized patients. Still, we need to establish that confidence and effectiveness persist into the third year clinical courses. A future survey of clerkship directors may provide useful information on the outcome of our learners over time.

We view the full implementation of this curriculum as a positive experience for all participants and expect improved outcomes in our students' physical examination skills after the experience.

Medical schools need to improve the clinical skills of their students that continue to go unobserved and deficient in a significant number of cases. Our health care system calls for improved clinical skills of our graduates in our managed care environment, and a larger representation of qualified generalists in our physician workforce. We can address these problems by reviewing our curriculum and giving introductory clinical skills courses effective instructional and evaluation strategies. There is plenty of evidence on the effectiveness of well planned courses that incorporate adult learning theory, with solid instructional principles to improve the outcomes of our graduates. Reviewing and developing clinical skills curricula will address these issues and aid in achieving our institutional and societal goals.

Adnowledgements

This curriculum was possible thanks to the support and advise of the faculty at the Michigan State University Primary Care Faculty Development Fellowship. The invaluable assistance of Dr. William Anderson and Dr. Gary Ferenchick is greatly appreciated.

Bibliography

1. Barrows, H. S., and Pickell,G.C. Developing Clinical Problem - Solving Skills. New York, N.Y.: W.W. Norton & Company; l 991.
2. Educating Medical Students: Assessing Change in Medical Education -The Road to Implementation, The ACME-TRI Report. Academic Medicine, 1993, 68 (ó), Sl-S67.
3. Stillman, P.L., Regan, M.B., Swanson, D.B., Case, S., McCahan, J., Feinblat, J., Smith, S. R., Willms, J., and Nelson, D. V. An assessment of the clinical skills of fourth- year students at four New England Medical Schools. Academic Medicine, 1990, 65 (5), 320 326.
4. Johnson J.E., Carpenter J.L. Medical house staff performance in physical examination. Arch Intern Med, 1986, 146, 937 - 941.
5. Li, J.T.C. Assessment of basic physical examination skills of Internal Medicine residents. Academic Medicine, 1994, 69 (4), 296-299.
6. The Clinical Skills Assessment Alliance. Academic Medicine, 1994, 69 (4), 285-287.
7. Council on Graduate Medical Education Sixth Report. Managed Health Care: Implications for the Phvsicians Workforce and Medical Education. US Department of Health and Human Services, September, 1995.
8. Greer, D.S., Bhack, K.N., and Zenker, B.M. Comments on the AAMC Policy Statement recommending strategies for increasing the production of generalist physicians. Academic Medicine, 1994, 69 (4), 245-260.
9. AAMC Policy on the Generalist Physician, Association of American Medical Colleges. Academic Medicine, 1993, 68 (1), 1 -5.
10. Wasson, J., Sox, H.C., Tomokins, R.K., Walsh, B.T., Peterson, J., and Rund, l).A. Teaching physical diagnosis: the effect of a structured course taught by medical students. Journal of Medical Education, 1976, 51, 1014-1015.
11. Friedman, S.A., and Judge, R.D. Using student produced mediated instruction in teaching physical diagnosis. Journal of Medical Education, 1976, 51, 596-597.
12. Barnes, H.V., Albanese, M., Schroeder, J., and Reiter, S. Senior medical students teaching the basic skills of history and physical examination. Journal of Medical Education, 1978, 53, 432-434.
13. Escovitz, E. S. Using senior medical students as clinical skills teaching assistants. Academic Medicine, 1990, 65 (12), 733-734.
14. Solomon, R., Jones, J., Holmes, M.M., and Hoppe, R. Teaching medical students a developmental approach to examining patients. Academic Medicine, 1991,66 (2), 77-78.
15. Klachko, D.M., and Reid, J.C. The effect on medical students of repetition of a physical examination routine. Journal of Medical Education, 1976, 5 l, 670-672.
16. Stillman, P.L., Ruggill, J.S., Rutala, P.J., and Sabers, D.L. Patient Instructors as teachers and evaluators. Journal of Medical Education, 1980, 55, 186-193.
17. Barrows, H. S. An overview of the uses of standardized patients for teaching and evaluating clinical skills. Academic Medicine, 1993, 68 (6), 443-474.
18. Elliot, D.L., and Hickman, D.H. Evaluation of physical examination skills. JAMA, 1987, 258 (23), 3405-3408.
19. Stillman, P.L., Swanson, D.B. Ensuring the clinical competence of medical school graduates through standardized patients. Arch Intern Med, 1987, 147, 1049-1052.
20. Kowlowitz,V., Hoole,A.J., and Sloane, P.D. Implementing the objective structured clinical examination in a traditional medical school. Academic Medicine, 1991, 66 (6), 345- 347.
21. Berg,D., Sebastian, J., and Heudebert,G. Development, implementation and evaluation of an advanced physical diagnosis course for senior medical students. Academic Medicine, 1994, 69 (9), 758-764.
22. Curry, R.H., and Makoul,G. An active approach to basic clinical skills. Academic Medicine, 1996, 71 (1), 41 -44.
23. Mann, K.V. Educating medical students: lessons from research in continuing medical education. Academic Medicine 1994, 69 (1), 41-47.

Journal Watch:

Cáncer treatment by targeted drug delivery to tumor vasculature in a mouse model

Resumido por Eduardo A. Santiago-Delpín
(Science, 1998, 279:377-380)

Arap y colaboradores utilizaron bibliotecas de fagos para aislar péptidos que migran directa y específicamente a los vasos sanguíneos de tumores. Al acoplar la droga anticáncer doxorubicin, dos de dichos péptidos, uno conteniendo un motivo arginina-glicina-aspartato, y otro, con glicina y arginina ambos que se adhieren a la integrina, aumentaron la eficiencia de adherencia de la droga directamente a xenoinjertos de cáncer de mama humano en ratones desnudos, a la vez que disminuyeron marcadamente la toxicidad. Retratos en el artículo utilizando tinciones con inmunohistoquímica luego de la inyección intravenosa, demuestran la marcada atracción de la droga por el xenotrasplante de cáncer de mama. Estos resultados indican que es posible desarrollar estrategias de quimioterapia directa a tumores basadas en la expresión selectiva que tienen algunos tumores de algunos receptores de integrinas y otras moléculas celulares. Este estudio complementa otros estudios utilizando técnicas similares pero con anticuerpos acoplados a quimioterapia o a inmunotoxinas.

POEMA

Recién Nacido

Por Dra. Eloísa Muñoz Dones de Carrascal

Como la hermosa flor que abre sus pétalos
vienes al mundo,
con tu dulzura y mansedumbre,
llenando de paz y amor
el hogar que te acoge, como un
símbolo de esperanza y felicidad.

Llenando de ilusiones todos los corazones,
se borra el odio y nace la alegría,
todos esperan un futuro acogedor.
Eres un ser indefenso,
totalmente dependiente,
pero eres lo más grandioso, el milagro
más grande de la humanidad.

Tan pequeño y tan fuerte,
capaz de desarrollarte
en el ser más potente y más sabio.

Eres el llamado a regir los futuros
destinos del hogar, que te acoge
con alegría y emoción,
dando gracias al Sumo Creador
por el regalo que ha bendecido
a la familia.

Eres nuestra responsabilidad
y somos los que tenemos
que luchar por ti,para ofrecerte
un mundo lleno de confianza,
integridad y de grandes valores humanos
para que puedas desarrollarte a plenitud,
para crear un mundo mejor, llenando
tu cometido en la vida,
usando las mejores armas;
amor paz y libertad.

Con tu ternura, logras doblegar
las voluntades de los más poderosos
y a cambio sólo ofreces,
tu inocencia y tu belleza angelical,
como emblema de cariño
para toda la humanidad.

Eres recién nacido,
la gloria del mañana,
el regalo de amor que Dios
nos otorga a manos llenas
para el bien de todos...

Correspondencia Recibida:

Abril 12 1998

Pedro M. Mayol M.D.
Boletín AMPR
Asociación Médica de Puerto Rico
Apartado de Correos 9387
San Juan, Puerto Rico 00908-9387

Re: Carta al Editor

Estimado Dr. Mayol

Leí con gran interés el artículo del Dr. Luis Acabá que apareció en el **volumen 89,10-11-12,1997** del Boletín. El Dr. Acabá describe la nueva unidad de trasplantes de médula ósea en el Hospital Universitario. El segundo párrafo habla de la historia de los trasplantes en Puerto Rico y dice - "The history of BMT for adults in PR is very limited". Aun cuando esta aseveración fuera correcta, no se debe olvidar que sí existe un historial que recordar y del cual podemos sentirnos orgullosos.

Entiendo que posiblemente el primer trasplante en nuestra isla lo practicó el Dr. Ramón M. Suárez. No tengo referencias apropiadas para este dato histórico y me interesaría saber si algún miembro de la AMPR pueda proveerlas. Años más tarde, comenzando en el 1969, el Dr. Norman Maldonado (entonces Director de la Sección de Hematología Hospital Universitario) llevó a cabo varios trasplantes. Yo tuve la oportunidad de participar en el equipo de trabajo para dos de éstos. Recuerdo que entre otros también participaron los doctores Ezequiel Rivera Rodríguez y Pedro Juan Santiago Borrero. El primero fue un joven paciente con una Aplasia Medular. La donante para este trasplante fue su hermana que era enfermera en el Hospital de Veteranos y quien trágicamente murió años después de Leucemia Mielógena Crónica. El segundo fue un paciente pediátrico con una Leucemia Aguda. El donante fue su gemelo idéntico y el trasplante tuvo éxito.

Estos trasplantes son altamente significativos ya que treinta años atrás muy pocos centros a nivel mundial llevaban a cabo este procedimiento. En Estados Unidos la mayoría de los programas de trasplantes de las instituciones que hoy se consideran "centros de excelencia en trasplantes" no existían para esa época. Fuimos pioneros en Puerto Rico. No olvidemos esa historia.

Felicito al Dr. Acabá, al personal de la nueva unidad de trasplantes en el Hospital Universitario, y a todos los responsables por su creación y funcionamiento y les deseo mucho éxito!!!

Sinceramente.
Antonio J Grillo-López. M. D.

18 de marzo de 1998

Pedro M. Mayol,M.D.
Editor Boletín de AMPR
Apartado 9387
San Juan, P. R. 00908

Sr. Editor:

Se han publicado dos(2) artículos en el Boletín de la AMPR, Vol. 89, Núm. 10-11-12 octubre-noviembre-diciembre 1997, a los cuales desearía añadir lo siguiente:

1) Acute dissection of the thoracic aorta: Experience at the P. R. Medical Center. - César A. Vázquez MD, Héctor Delgado Osorio MD (Pág. 161)

Sólo como motivo de carácter histórico deseo señalar que, en Puerto Rico, el primer caso de aneurisma disecante de la aorta descendente torácica se diagnosticó y se operó en Doctor's Hospital en el año 1958. El Dr. Francisco Raffucci fue el cirujano, asistido por el Dr. José S. Licha. El diagnóstico fue uno clínico y lo hizo el que suscribe en un varón de unos 45 años que venía sufriendo de hipertensión. Había desarrollado un dolor en el área media de la espalda, no fijo, y en el examen físico se descubrió matidez en la base del pulmón izquierdo. Se le practicó una toracentesis la cual produjo sangre pura. El diagnóstico se confirmó durante la operación. Cuando ya se había logrado cerrar la rotura, el aneurisma rompió por otra parte y esta vez el paciente no lo pudo sobrevivir.

2) Adult bone marrow transplantation in Puerto and future. - Luis Acabá MD, FACP (Pág. 211).

Como en este artículo se hace referencia al pasado, creo mi deber informar que el primer transplante de médula ósea que se hizo en Puerto Rico lo logró el Dr. Rodrigo Menéndez Corrada en el viejo Hospital San Patricio, de la Administración de Veteranos, estimo que a principios de la década del '60. Me consta que el paciente sobrevivió la operación por varios años. El Dr. Menéndez Corrada, hematólogo, fue el que organizó la Sección de Hematología en el hospital mencionado. Si es de interés de los autores del artículo conocer más detalles del caso, les sugiero comunicarse con él.

Sirva ésta, además, para felicitar a los autores de ambos artículos. Para mí son valiosos y de interés.

Sinceramente,
José M. Torres-Gómez, MD FACP, FACC



Descubre cómo puedes añadirle vida a tus años deliciosamente...
Muchas veces nuestra dieta o estilo de vida no nos ayuda a alimentarnos como es debido. Pero ahora existe Sustacal, que suple una nutrición total y balanceada completando el régimen que necesitamos diariamente.
• Un balance completo de proteínas, carbohidratos, vitaminas y minerales.
• De 20 a 30% del requerimiento diario de los nutrimentos esenciales para lograr una dieta balanceada.
• Tres deliciosos sabores: Vainilla, Chocolate y Fresa.
Más Proteínas con Menos Grasa
Sustacal
Complete liquid nutrition
High Protein Formula
chocolate
vanilla
Delicioso suplemento nutricional listo para tomar
Sustacal.
Añade vida a tus años

SOCIOS NUEVOS

ENERO - MARZO 1998

Ingresos:

Activos

Brenda Mirabal Rodríguez, M.D.
Mercedes Blanche Herrera, M.D.
Marina Alemanas Morales, M.D.
Jaquelin Colón Marín, M.D.
Efraín Feliciano Guzmán, M.D.
Rafael Soto Linares, M.D.
Genaro R. Bou Umpierre, M.D.
José Rivera Viera, M.D.
María P. Casado García, M.D.
Jorge Rafael Toro Ramírez, M.D.
Carmen Y. Santiago Aponte, M.D.

Re-Ingreso:

Activos

Néctar P. de la Rosa, M.D.
Benjamín García Medina, M.D.
Nelson Fernández Blasini, M.D.
Manuel López Matos, M.D.
Roberto Gardón Alvarez, M.D.
Hilda Rivera Tubens, M.D.
Mario R. García Palmieri, M.D.
Edwin Soto Tapia, M.D.
Restituto Alvarez Reid, M.D.
Ana V. López de Alvarez, M.D.

El Ácido Fólico y la Prevención de Defectos del Tubo Neural (NTD)

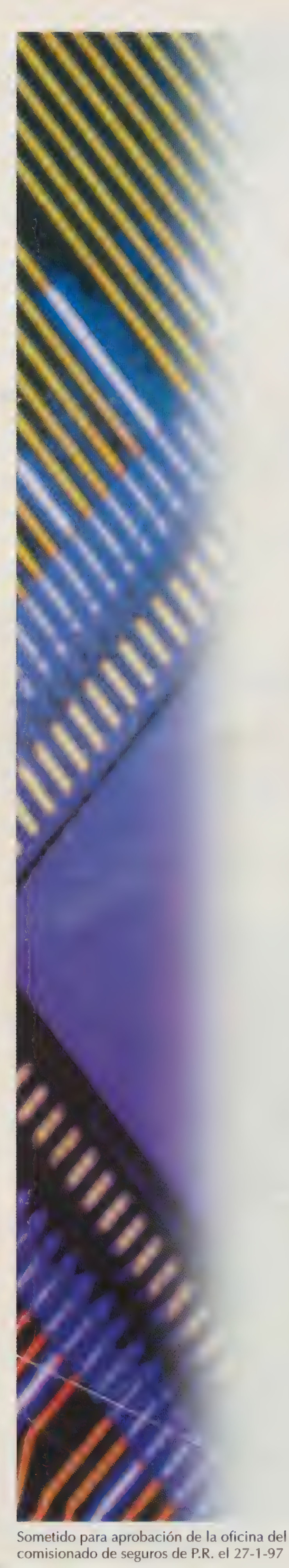
El ácido fólico, vitamina del complejo B, está relacionado con el metabolismo de aminoácidos y la síntesis de RNA y DNA. De no estar presente en cantidades suficientes al momento del cierre del tubo neural en el embrión (día 26-28 del período de gestación) se afecta la formación de tejido, provocando diferentes defectos. Algunos de estos defectos son la condición de Anencefalía (ausencia de cerebro), y Meningocele o Espina Bífida. Los bebés que nacen con estos defectos van a presentar afección simultánea de los sistemas nervioso central, musculoesqueletal, génitourinario y problemas de aprendizaje asociados. A tales efectos van a necesitar de servicios de salud especializados y sub-especializados. Esto representa una carga emocional, social y económica para los padres.

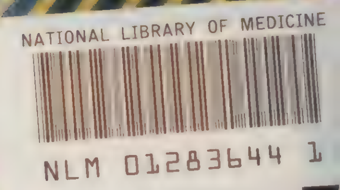
En Puerto Rico, anualmente 1.6 casos se estiman por cada mil nacimientos vivos, lo que equivale al doble de la incidencia en Estados Unidos.

Estudios realizados por diferentes investigadores han comprobado que la ingesta de 0.4 mg de ácido fólico y consistentemente durante la edad reproductiva, 10-50 años, disminuye hasta en un 50% la ocurrencia de algunos defectos del tubo neural (NTD). También estos estudios han comprobado que la ingesta de 4 milígramos de ácido fólico diarios reduce en 70% la recurrencia de NTD en mujeres que han tenido un bebé con uno de estos defectos.

Los cereales Kellogg's Corn Flakes y Kellogg's Product 19 proveen el 45% y 100% respectivamente del ácido fólico que se necesita diariamente.







UNA CONEXION



¡SALUDABLE!

Siempre a la vanguardia de la tecnología, **TRIPLE-S** le provee a los médicos y dentistas de su red el **SISTEMA ELECTRONICO DE SALUD PROFESIONAL**.

SES-PROFESIONAL es un avanzado programa computadorizado que agiliza el proceso de facturación y pago de reclamaciones, a la vez que optimiza la comunicación entre **TRIPLE-S** y sus proveedores.

Más de 3,200 profesionales de la salud ya están conectados a **SES PROFESIONAL**, convirtiéndolo así en una herramienta vital para administrar sus oficinas de manera más eficiente y garantizar un servicio de calidad a sus pacientes.

Por eso, SES es, ¡La conexión saludable!

Línea Directa de Asistencia 793-5223



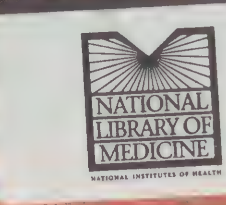
Sometido para aprobación de la oficina del comisionado de seguros de P.R. el 27-1-97

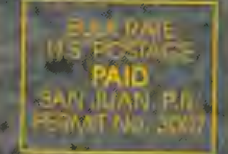
Boletín

VOL. 90 ● NUM. 4 - 5 - 6 ● ABRIL - MAYO - JUNIO 1998



ASOCIACION MEDICA de puerto rico





...TOGRAFIA POR: DR. ANSELMO MIRANDA MARTIR

ASOCIACION MEDICA DE PUERTO RICO

BOLETIN

VOL. 90 • NUM. 4 - 5 - 6 • ABRIL - MAYO - JUNIO 1998

OFICINAS ADMINISTRATIVAS

Asociación Médica de Puerto Rico
Ave. Fernández Juncos Núm. 1305 • Apartado 9387
San Juan, Puerto Rico 00908 • Tel (787) 721-6969

SUBSCRIPCIONES Y ANUNCIOS

Asociación Médica de Puerto Rico
Apartado 9387 • San Juan, P.R. 00908 • Tel. (787) 721-6969

Publicación trimestral - $40.00 anuales. El Boletín se distribuye a todos los miembros de la Asociación Médica de Puerto Rico como parte de su cuota anual.
Todo anuncio que se publique en el Boletín de la Asociación Médica de Puerto Rico deberá cumplir con las normas establecidas por la Asociación Médica de Puerto Rico y la Asociación Médica Americana.
La Asociación Médica de Puerto Rico no se hace responsable por los productos o servicios anunciados. La publicación de los mismos no necesariamente implica el endoso de la Asociación Médica de Puerto Rico.
Todo anuncio para ser publicado debe reunir las normas establecidas por la publicación. Todo material debe entregarse listo para la imprenta y con sesenta días de anterioridad a su publicación. La AMPR no se hará responsable por material y/o artículos que no cumplan con estos requisitos.
Todo artículo recibido y/o publicado está sujeto a las normas y reglamentos de la Asociación Médica de Puerto Rico. Ningún artículo que haya sido previamente publicado será aceptado para esta publicación. La Asociación Médica de Puerto Rico no se hace responsable por las opiniones expresadas o puntos de vista vertidos por los autores, a menos que esta opinión esté claramente expresada y/o definida dentro del contexto del artículo.

Boletín de la Asociación Médica de Puerto Rico is published quarterly for $40.00 per year by Asociación Médica de Puerto Rico, 1305 Fernández Juncos Ave. P.O. Box 9387, San Juan, Puerto Rico 00908.
"POSTMASTER" Send address changes to Boletín Asociación Médica de Puerto Rico, 1305 Fernández Juncos Ave. P.O. Box 9387, San Juan, Puerto Rico 00908.

Catalogado en Cumulative Index e Index Medicus.
Listed in Cumulative Index and Index Medicus.
No. ISSN - 0004-4849

CONTENIDO

ampr

FUNDADO 1903

JUNTA DE DIRECTORES 1998

Gonzalo González Liboy, M.D.
Presidente

Luis A. Parés Martínez, M.D.	*Presidente Electo*
Jaime M. Díaz Hernández, M.D.	*Presidente Saliente*
Sylvia A. Fuertes Thomas, M.D.	*Secretaria*
José I. Iglesias, M.D.	*Tesorero*
Luis Aponte, M.D.	*Vicepresidente AMPR*
Roberto Rodríguez Martínez, M.D.	*Vicepresidente AMPR*
Carlos García Goyco, M.D.	*Vicepresidente AMPR*
Miguel A. Cubano, M.D.	*Pres. Cámara Delegados*
Eladio Santos Aponte, M.D.	*Vicepres. Cámara Delegados*
Filiberto Colón Rodríguez, M.D.	*Delegado AMA*
Emilio A. Arce, M.D.	*Delegado AMA*
Calixto E. Pérez Prado, M.D.	*Delegado Alterno AMA*
Antonio De Thomas, Jr., M.D.	*Delegado Alterno AMA*

PRESIDENTES DE DISTRITOS Y CONSEJOS

Héctor Hernández Ortega, M.D.	*Presidente Dtto. Noreste*
Luis H. Rodríguez García, M.D.	*Presidente Dtto. Sur*
Jerry Ramos Rodríguez, M.D.	*Presidente Dtto. Guayama*
Rafael Fernández Feliberti, M.D.	*Presidente Dtto. Este*
José Martí Núñez, M.D.	*Pres. Consejo Política Pública y Legislación*
Santiago N. Sallaberry, M.D.	*Pres. Consejo e Instituto EMC*
Alicia Feliberti, M.D.	*Pres. Consejo de Serv. Médicos*
Gerardo Sanz Ortega, M.D.	*Pres. Consejo Etico-Judicial*
Carlos Gadea Mora, M.D.	*Pres. Consejo de Salud Pública y Medicina Gubernamental*
Raúl G. Castellanos Bran, M.D.	*Pres. Consejo Relaciones y Servicios Públicos*
Verónica Rodríguez, M.D.	*Pres. Comité de Afiliación y Credenciales*
Juan G. Figueroa Longo, M.D.	*Pres. Comité Científico*
Pedro M. Mayol, M.D.	*Pres. Junta Editora Boletín*
Francisco Rivera Lizardi, M.D.	*Pres. Junta Editora Prensa Médica*
José C. Román De Jesús, M.D.	*Pres. Comité Historia, Cultura y Religión*
Luis A. López Sánchez, M.D.	*Pres. Comité Calidad Ambiental*
José A. Rodríguez Ruiz, M.D.	*Pres. Comité Medicare*
Judith Román, M.D.	*Pres. Comité de Enlace con los Estudiantes de Medicina*
Sara B. Lebrón de Sanz, M.D.	*Pres. Comité de Responsabilidad Profesional*
Valeriano Alicea Cruz, M.D.	*Pres. Comité Esp. Médicas*
Luis A. Izquierdo Mora, M.D.	*Pres. Comité Asesor del Presidente*
Ovidio Rodríguez, M.D.	*Pres. Comité Planes Prepagados*
Francisco E. Colón Ramos, M.D.	*Pres. Comité Calidad de Vida*
Humberto Lugo Vicente, M.D.	*Pres. Comité Internet*
José C. Román de Jesús, M.D.	*Pres. Comité de Enlace Interamericano*
José R. Villamil, M.D.	*Pres. Comité del Médico Impedido*
Ramón Cuevas Natal, M.D.	*Pres. Comité Premios Bohique*
Luis A. Parés Martínez, M.D.	*Pres. Comité de Convención*
Jorge Colón Vélez, M.D.	*Pres. Comité de Biblioteca*
José M. Torres Ramos, M.D.	*Pres. Clínicas Externas*



Jaime M. Díaz Hernández, M.D.	*Pres. Comité Act. Musicales*
Carlos García Goyco, M.D.	*Pres. Comité Reforma de Salud*
Julio Rivera Ilarraza, M.D.	*Pres. Comité de Enlace con Agencias Federales*

PRESIDENTES DE SECCIONES

Francisco de la Torre, M.D.	*Alergia e Inmunología Clínica*
Luis Cumming Carrero, M.D.	*Anestesiología*
Amarilis Silva, M.D.	*Cirugía de Manos*
Luis E. Iguina Mella, M.D.	*Cirugía General*
José Ismael Iglesias, M.D.	*Cirugía Plástica*
Alma Cruz Santana, M.D.	*Dermatología*
Carlos H. Ramírez Ronda, M.D.	*Infectología*
Dwight Santiago Pérez, M.D.	*Medicina Deportiva*
Alicia G. Feliberti, M.D.	*Medicina de Emergencia*
Jaime M. Díaz Hernández, M.D.	*Medicina de Familia*
Emma Lou Carreras, M.D.	*Fisiatría*
José J. Corcino, M.D.	*Hematología y Oncología*
Raúl G. Castellanos Bran, M.D.	*Medicina General*
Félix Matos, M.D.	*Medicina Industrial*
Sylvia A. Fuertes, M.D.	*Medicina Interna*
Ramón Figueroa Lebrón, M.D.	*Neumología*
Heriberto Acosta, M.D.	*Neurología*
Manuel Náter Orsini, M.D.	*Obstetricia y Ginecología*
Antolín Alvárez Pont, M.D.	*Oftalmología*
José Montañez Huertas, M.D.	*Ortopedia y Traumatología*
Mariano González Diez, M.D.	*Otolaringología, Cirugía de Cabeza y Cuello*
José L. Miranda, M.D.	*Patología*
Juan F. Jiménez, M.D.	*Pediatría*
Carmen Zoraida Sanz, M.D.	*Psiquiatría*
Julio Rojo, M.D.	*Radiología*

Editorial:

Un saludo muy cordial a todos nuestros lectores

Invitamos a todos los lectores a que disfruten de la lectura de la sección "El Boletín y su Historia". Las palabras que se incluyen en esta sección son seleccionadas de artículos publicados en el "Boletín" en sus primeras ediciones a principios de siglo. Las palabras y pensamientos de los múltiples autores que se han presentado nos obligan a reestablecer nuestra relación como galenos con la historia de la medicina, nuestra relación como practicantes de la salud con la práctica médica del momento y como seres humanos con la temporalidad de nuestras vidas y la inmortalidad de la palabra escrita.

La selección de los artículos de esta sección ha sido particularmente interesante y frecuentemente difícil para nosotros. Es un genuino placer vivir la palabra escrita de nuestros colegas médicos a principios de siglo y reflexionar sobre la falta de temporalidad o quizás en la universalidad de sus ideas, pero más importante el entusiasmo y energía que se desprenden de sus iniciativas y proyectos en ese momento. En adición, se hace claro que una de las tareas indelegables de la clase médica es ejercer su liderato en fomentar, diseminar y mantener la salud de nuestro pueblo de forma desinteresada. La historia nos juzgará. En la carrera de relevo de la historia médica de nuestro país se nos ha entregado el batón, no lo dejemos caer.

Agradecemos su interés y lectura de éste, SU BOLETIN.

Mensaje:

La Educación Médica

Por: Gonzalo González Liboy, M.D., FACP
Presidente AMPR

La clase médica se conoce generalmente por dos vocablos, uno romano derivado del latín "medeor", que significa sanar. De aquí se deriva nuestro conocido "medicus" o médico. Debido a la prominencia del médico en la sociedad como el conocedor de vastas ciencias, el término doctor se nos ha aplicado indistintamente. El vocablo doctor se deriva de "docere", lo cual significa enseñar, como es de todos conocido.

Tanto en la Declaración de Ginebra de la Organización Mundial de la Salud en el 1948 como el clásico Juramento Hipocrático, nuestra profesión ha tenido a través de los siglos la responsabilidad de difundir nuestros conocimientos médicos tanto a los colegas de nuestra profesión como a los pacientes y al público en general.

Este precepto nos obliga a aumentar constantemente nuestros conocimientos médicos a través del estudio continuo en conjunción con médicos de alto calibre intelectual y nobles estándares éticos. Es imprescindible el que intercambiemos información y experiencias con todos nuestros colegas médicos.

El Boletín de la Asociación Médica de Puerto Rico desde el momento de su primera publicación ha servido como vehículo para la difusión de estas ideas. La Asociación Medica de Puerto Rico ha descargado su responsabilidad como vocero de estos ideales educativos a través de sus noventa y seis (96) años de existencia.

La Asociación Médica de Puerto Rico endosó la creación de un organismo para la reglamentación de la práctica de la medicina en Puerto Rico, vía del Dr. Ramón M. Suárez Calderón. Esta entidad se convierte en ley en el 1931. El propósito principal es el de reglamentar la práctica de la medicina en Puerto Rico a la misma vez que habría de vigilar para que se cumplan los requisitos básicos de fuerza, honestidad y excelencia didáctica en los programas de educación médica en Puerto Rico.

A través de toda su historia la Asociación Médica ha tenido como propósito esencial de su existencia el difundir el conocimiento médico a través de la educación médica continuada. Con este propósito se crea el Boletín de la Asociación Médica de Puerto Rico, con apenas un año de haberse creado nuestra Institución en el 1903.

El Instituto de Educación Médica ha demostrado su excelencia como vehículo de diseminación educativa, con una calidad tan alta que ha sido reconocido por ACCME ("Accreditation Council for Continuing Medical Education"), como la institución de más alto prestigio en la educación médica en los Estados Unidos en el 1997. Este esfuerzo se lo debemos a todos los Pasados Presidentes del Instituto, pero en especial al Dr. Jaime M. Díaz Hernández, Pasado Presidente de nuestra organización, y al actual Presidente, Dr. Santiago N. Sallaberry.



El compromiso de la Asociación Medica de Puerto Rico con la educación médica continua no se limita al papel de proveedor de estos servicios. La Asociación Médica ha de velar porque los estatutos legales que deben regir la educación médica continua y las instituciones que supervisa dicha institución jueguen el papel principal de facilitadores de esta actividad didáctica.

Nuestro Boletín Médico podría convertirse en un vehículo adicional para obtener créditos educativos a través de sus publicaciones. En la actualidad nuestro Boletín es la única publicación en nuestra Isla que está reconocida por la Biblioteca Nacional de Medicina en Bethesda, Maryland, y como tal la única publicación médica incluida en el Index Médico.

Para mantener esta visión en la educación médica, nuestra Asociación habrá de continuar luchando. Nuestra visión y derrotero está trazado rumbo a ese ideal, iremos con fe y con ahínco, pues nos asiste la razón.

El Boletín y su Historia:

Medicina Tropical

Editorial Boletín Asociación Médica de Puerto Rico - Abril 1904

Por el Dr. J.N. Carbonell

Al crearse la Asociación Médica de Puerto Rico, uno de sus principales objetivos, quizás el más importante de todos, fue, como dice el Reglamento de ella, "dar impulso a la Ciencia Médica insular", y para esto creóse al mismo tiempo el "Boletín de la Asociación", que si algún mérito práctico ha de tener, será indudablemente el que le concedan todos aquellos que entre nosotros se ocupen en publicar sus observaciones y en emitir sus juicios acerca de aquellos enfermos que asistidos en nuestra práctica presenten algo de especial, algo de característico dentro de la faz propia de nuestra Patología tropical.

Sin este esfuerzo individual, pero colectivo a la vez, es muy difícil, si no imposible, formar doctrina, y en nuestra Patología regional se encontrarán siempre las densas obscuridades que se advierten todavía, mientras este esfuerzo no se realice de una manera tenaz y sostenida.

Es muy cierto que por algunos de los que nos han precedido en la labor penosa del ejercicio diario de nuestra profesión, se ha intentado muchas veces emprender esta obra, como lo prueban los magníficos trabajos que existen diseminados en diversas publicaciones de esta índole, que tuvieron una vida lánguida y una duración efímera, sin duda por no encontrar terreno abonado ni ambiente propio para el desenvolvimiento de tales estudios.

Pero los tiempos han cambiado mucho y a la inercia de un gobierno que apenas se preocupaba de la salud pública, ha sucedido otro que consagra especial y cuidadoso interés a este ramo de su Administración, concediendo a la higiene el papel cada vez más preponderante que tiene en la sociedad moderna: "gracias á la higiene, higiene del terreno orgánico, higiene de los medios, es como podemos escapar de las enfermedades llamadas evitables."

En este sentido, séame permitido tributar mis más sinceros elogios a nuestra Junta Superior de Sanidad, que pone todos sus empeños en alcanzar tamaño triunfo como el conseguido ya, logrando exterminar entre nosotros ciertas enfermedades que eran antes el terror de todos.

Yo alcanzo a ver en esta acción del gobierno un marcado estímulo a los hombres estudiosos y observadores de nuestra profesión y a ese estímulo debemos responder seriamente.

Por eso, entiendo que la Asociación, al crearse en momentos tan oportunos, tiene su vida asegurada por poco que nos empeñemos en ello, porque la atención del gobierno habrá de fijarse en nosotros y vendrá a auxiliarnos en esta labor noble y desinteresada.

Ahora bien: la higiene para llegar a su

(Continúa en la pág. 57)

El Boletín y su Historia:

momento práctico, tiene necesidad de conocer la fórmula última de una serie de conocimientos, entre los que ocupa preferente y distinguido lugar la Patología, y sabido es que existen muchas incógnitas en la intertropical, las cuales están demandando nuestro estudio para que puedan ser resueltas.

Véase como se expresa Neveu-Lema're en su reciente obra sobre *Los hematozoarios del paludismo*:

"Existen probablemente enfermedades tropicales cuya etiología es todavía muy obscura y que son tal vez producidas por organismos que se aproximan más o menos a los hematozoarios.

El reino de las bacterias ha llegado a su apogeo y comienza el de los protozoarios. Desde los descubrimientos de Pasteur, las bacterias han sido objeto de incesantes estudios y dado lugar a trabajos considerables, mientras que el estudio de los protozoarios estaba completamente abandonado por los médicos. El hematozoario del paludismo descubierto por Laveran, era el único protozoario patógeno conocido.

Recientemente la leucemia se ha atribuido a protozoarios que viven como pará sitos en los leucocitos, el bocio a parásitos análogos a los hematíes. Finalmente, los estudios que se practican actualmente con la mayor actividad, sobre todo en el extranjero, demostrarán probablemente el papel de nuevos protozoarios parásitos en ciertas enfermedades tropicales, tales como la fiebre biliosa, hemoglobinúrica, el kala-azar y el beriberi".

Hasta que no dominó en el mundo científico la doctrina etiológica imperante hoy, y que atribuye la causa de las fiebres a un agente patógeno cuya evolución en el organismo invadido, explica las determinaciones anatomo-clínicas con sus caracteres específicos, cuan difícil era llegar a un acuerdo con la separació n de ciertas entidades morbosas, y de ahí lo mucho que se discutió para separar de las formas graves del paludismo, la fiebre amarilla, la remitente biliosa y la fiebre tifoidea de los países templados.

Demostrada la especificidad de algunas pirexias intertropicales, cabe desde luego afirmar que toda fiebre, como entidad nosológica, es función de un agente patógeno y como entidad clínica representa la reacción del organismo invadido por el microorganismo específico, entrando como causas secundarias en la producción de estos procesos morbosos, las condiciones de clima, medio social, predisposición, constitución médica, etc.

He fijado mi atención, al apuntar estas ideas generales, principalmente en las fiebres, por encontrarse en nuestro país una serie indeterminada de ellas no clasificadas todavía, por faltar el estudio de sus lesiones propias y de sus agentes específicos. Para evidenciar y enseñar el extenso e inexplorado campo de nuestra Patología insular, tenemos mucho terreno virgen que recorrer y que es preciso cultivar por medio de la observación clínica y del estudio de la etiología de esas especies morbosas, a fin de establecer un diagnóstico exacto y de obtener mayores ventajas en el tratamiento curativo y profiláctico de todas ellas.

De igual manera y con el mismo fin deberíamos llevar estas investigaciones a otras tantas enfermedades parasitarias que tienen su asiento en nuestras latitudes y que son motivo de estudio en otros países; con lo cual no harí amos mas que seguir la senda trazada por los brillantes trabajos emprendidos y realizados por la Escuela de Medicina Tropical, de Liverpool, que tantos progresos ha determinado en el conocimiento de muchas enfermedades de estas regiones.

Editorial: Boletín Asociación Médica de Puerto Rico
Volumen 2, No. 16, Abril 1904

Estudios Originales:

Indicadores de ansiedad y depresión en sujetos con diferentes tipos de alimentación: *vegetarianos y omnívoros*

Jenny Rodríguez Jiménez, M.S., M.S.W.,Ph.D.,*
*José R. Rodríguez, M.D., M.P.H.,Sc.D.,Ph.D.**,*
*Michael J. Gonzaléz, M.S., Sc.D., Ph.D.,F.A.C.N.****

Resumen: *En el siguiente estudio, pionero en su área, investigó si los tipos de alimentación (vegetarianas y no-vegetarianas) influyen en los estados de ansiedad y depresión de los sujetos. La muestra seleccionada estuvo constituida por 80 sujetos de 25 a 70 años de edad. Se realizó un análisis de covarianza con el propósito de conocer si existen diferencias significativas en los niveles de ansiedad y depresión entre los grupos con diferentes tipos de alimentación: vegetarianos y omnívoros. Los resultados indican que las diferencias encontradas en las 3 pruebas psicológicas administradas (el Inventario IDARE1 e IDARE2, que miden ansiedad, y la Escala CES-D, que mide depresión) resultaron significativas. El nivel de significancia para la prueba IDARE1 fue de 0.005, para la prueba IDARE2 de 0.003 y a nivel de 0.004 para la prueba CES-D. Tanto el grupo que consumia carnes rojas y otras, como el grupo que consumia carnes blancas y pescado, obtuvieron las puntuaciones mas altas en las pruebas IDARE1, IDARE2 y la Escala CES-D, lo cual indica que estos grupos mostraban mayores indicadores de ansiedad y depresión. Por el contrario, los grupos que no ingieren carnes, (vegetarianos ovolá cteos y puros) obtuvieron los niveles de ansiedad y depresión mas bajos en estas pruebas. Los resultados sugieren que existe relación entre la ingesta de carnes y otros alimentos, y los niveles de ansiedad y depresión que experimentaron los sujetos bajo estudio. En el análisis dietario realizado a la muestra, se encontró además, que las dietas vegetarianas eran altas en vitaminas A, C y E. También proveían cantidades adecuadas de proteínas y hierro, pero por otro lado, el grupo vegetariano puro era deficiente en vitaminas B_{12}, calcio, zinc y bajo en colesterol. Los grupos omnívoros obtuvieron niveles adecuados de todos estos nutrientes excepto zinc, donde apuntaron por debajo de los grupos vegetarianos.*

INTRODUCCIÓN

Hoy día los profesionales de la salud y otros grupos de la población demuestran mayor interés en mantener una buena salud. Los estilos de vida y los hábitos dietarios se han encontrado que son vitales para mejorar la calidad de vida. La orientación a la población sobre que alimentos ingerir y en que proporciones es cada vez mas necesaria. Muchos grupos de la población están cambiando sus estilos de vida y sus hábitos dietarios por unos mas saludables de acuerdo a sus preferencias. Estas personas compran alimentos nutritivos y visitan los "Health Foods". Algunos de estos han reducido la ingesta de carne o son vegetarianos. En este estudio nos interesa investigar si los tipos de alimentación vegetarianas u omnívoras influyen en los estados de ansiedad y depresión de los sujetos.

Los estudios científicos evidencian los beneficios para la salud de una alimentación vegetariana junto con otros estilos de vida saludables, como lo son el no ingerir café, bebidas alcohólicas o gaseosas, comer alimentos poco nutritivos ("junk food"), así como el mantener un peso normal y un programa regular de ejercicios (1,2,3). Las investigaciones sostienen además que una alimentación vegetariana puede ser un factor fundamental para reducir enfermedades degenerativas como algunos tipos de cáncer, diabetes y enfermedades cardiovasculares (4,5).

Los vegetarianos ingieren más alimentos con un alto contenido de fibra, grasas polinsaturadas (omega-3), y vitaminas A (caroteno), C y E. Este tipo de alimentación incluye menos grasas saturadas, hierro y vitamina B_{12} (6,7,8,9,10).

Por otro lado, la alimentación vegetariana ha sido fuertemente criticada por algunos nutricionistas y otros profesionales de la salud (11,12,13). Ellos sostienen que ésta puede acarrear serios problemas a la salud si las mismas no están cuidadosamente planificadas. Apoyan su hipótesis en el hecho de que los vegetarianos totales (veganos) no consumen carnes rojas, pollo o pescado, los cuales son alimentos ricos en proteína, hierro, zinc y vitamina B_{12} (cobalamina), por lo que la ingesta de estos nutrientes puede ser inadecuada y ocasionar problemas de salud. Sin embargo, los estudios mencionados no han podido evidenciar enfermedades o problemas serios de salud en ésta población, y por el contrario, señalan efectos beneficiosos.

*Centro Caribeño de Estudios Postgraduados (CCEP); **Centro de Educación en Geriatría, RCM, UPR y CCEP; ***Escuela Graduada de Salud Pública, RCM, UPR

Partiendo de este planteamiento se investigó si se observan diferencias significativas en las pruebas que miden ansiedad y depresión cuando se comparan grupos de sujetos vegetarianos y no-vegetarianos. Además, se investigó cuales son los componentes de la alimentación básica de cada grupo y se comparó su contenido nutricional.

También se interesó conocer como se comporten otras variables independientes. Estas variables son: sexo, programa regular de ejercicios, uso de bebidas alcohólicas, café y cigarrillos, que en los estudios científicos, se ha encontrado que pueden tener alguna relación con los estados de ansiedad y depresión.

HIPOTESIS

Se establecieron las siguientes hipótesis:

H[1] Se observarán diferencias significativas en los niveles de ansiedad entre los grupos con diferentes tipos de alimentación (vegetarianas versus no-vegetarianas), lo cual sugiere que el consumo de carnes influye en los estados de ansiedad de los individuos.

H[2] Se observarán diferencias significativas en los niveles de depresión entre los grupos con diferentes tipos de alimentación (vegetarianas versus no-vegetarianas) lo cual sugiere que el consumo de carnes influye en los estados de depresión de los individuos.

H[3] La interacción de las covariables sexo, programa regular de ejercicios, uso de bebidas alcohólicas, café y cigarrillos ayudará a explicar las variaciones observadas en la variable dependiente (tipos de dieta) y reducirá la varianza residual.

H[4] El análisis del registro dietario nos permitirá establecer cuales son los hábitos dietarios de los diferentes grupos bajo estudio.

H[5] Se observarán correlaciones moderadas entre la ingesta de algunos alimentos como: las carnes, los azucares y harinas refinadas, y los estados de ansiedad y depresión.

H[6] El análisis nutricional del registro alimentario utilizando el programa computadorizado "Your Personal Nutritionist" nos permitirá conocer el nivel nutricional de los sujetos y si cumplen con los requisitos mínimos diarios (MDR, en inglés).

MÉTODO

Muestra

Los participantes fueron seleccionados entre las personas que asisten a los "Health Foods" que sirven comida vegetariana. A través de la guía telefónica se identificaron los pueblos de mayor cantidad de restaurantes vegetarianos ubicados en la Zona Metropolitana (San Juan, Carolina, Bayamón y Rio Piedras), en Puerto Rico, cuyos dueños fueron contactados. De aquellos que aceptaron participar en la investigación, se seleccionaron los cinco de mayor clientela.

A través de una carta informativa se orientó al público visitante sobre el propósito del estudio y los requisitos de participación. A los que aceptaron participar, se les llenó la hoja de consentimiento para su autorización. La carta también recogió información que nos permitió clasificar a los participantes de acuerdo a la edad, alimentación y años en esta dieta. Los participantes en el estudio fueron orientados sobre los procedimientos a seguir. La muestra total estuvo compuesta de 80 sujetos de ambos sexos los cuales tenían 25 años a 70 años de edad y llevaban 3 ó mas años en este tipo de alimentación. Se tomó esta edad como base ya que al alcanzar la vida adulta (alrededor de los 25 años) se observa mayor estabilidad fisiológica en el organismo, así como en sus hábitos de vida, incluyendo los dietarios (14). Tomando en consideración las clasificaciones de los estudios mencionados anteriormente (5,12,9) los participantes se clasificaron de la siguiente manera:

Alimentación vegetariana

Se dividió en dos niveles con 20 sujetos en cada grupo.

- *Alimentación vegetariana pura.* Consume vegetales, viandas, frutas naturales y proteína vegetal como granos, semillas, soya y otros afines.
- *Alimentación ovoláctea vegetariana.* Consume vegetales, viandas, frutas naturales y proteína vegetal como granos, semillas, soya y otros afines. Añade huevos, leche y sus derivados a la alimentación.

Alimentación no-vegetariana

Se dividió en dos niveles con 20 sujetos en cada grupo.

- *Alimentación que incluye carnes rojas y otras (omnívora total).* Añade carnes rojas y todo tipo de carnes a su alimentación.
- *Alimentación que incluye carnes blancas y pescado (omnívora limitada).* Añade solo carnes blancas (pollo, pavo) o pescado a su alimentación.

INSTRUMENTOS

Los instrumentos que se utilizaron fueron los siguientes:

Cuestionario de información del sujeto

Recogió los datos demográficos de cada participante e información sobre las otras variables que se deseaban investigar.

Cuestionario sobre hábitos alimentarios

El sujeto llenó este cuestionario donde anotó sus hábitos alimentarios. Este fue completado con la ayuda del entrevistador. Siguiendo la clasificación realizada por Kuzma et al.(10) el sujeto pudo seleccionar la frecuencia en que ingiere sus alimentos entre ocho alternativas (nunca o casi nunca, menos de una vez al mes, una o dos veces al mes, una o dos veces por semana, de tres a cuatro veces por semana, cinco a siete veces por semana, una por día, y mas de una vez al día). También el cuestionario proveyó para que el sujeto indicara la cantidad que ingiere de cada alimento. Como medidas se usaron: onzas, tazas, cucharas o cucharitas del sistema internacional de medidas. En algunas ocasiones las frutas y viandas se clasificaron como grande, mediana o pequeña.

Escala de Depresión del Centro Para Estudios Epidemiológicos (CES- D) y el Inventario de Autoevaluación IDARE

Se usaron estos dos instrumentos de evaluación psicológica para obtener indicadores de depresión y ansiedad en los sujetos. Ambos se encuentran validados para población puertorriqueña.

PROCEDIMIENTO

Con el propósito de conocer si los tipos de alimentación (vegetarianas y no-vegetarianas) influyen en los estados de ansiedad y depresión de los sujetos se realizó un análisis de varianza. En este análisis las variables dependientes ansiedad y depresión se midieron a través de dos instrumentos de medición psicológica; la Escala CES-D y el Inventario IDARE.

Se analizaron además, otras variables independientes que se trataron como covariables. Estas son:
sexo: Se clasificó como masculino o femenino.

programa regular de ejercicios: Se clasificó de acuerdo a leve, moderado o mucho según la guía de la Academia Nacional de las Ciencias (1989)(15).

uso de bebidas alcohólicas: Se clasificó de acuerdo a si tomaba, toma, o no toma. Si toma, se clasificó teniendo en consideración las Dietary Guidelines for America (1990) y los estudios de Ullmann, Phillips, Beeson, Dewey, Brin, Kuzma, Mathews, y Hirst (16). Esto es: leve (menos de un trago), moderado (un trago) y mucho (mas de un trago). Un trago equivale a:

Mujeres	Hombres	
1	2	cervezas 12 onzas
1	2	copas de vino 5 onzas
1	2	copitas de licor (tequila, whiskey, ron) 1 1/2 onzas

café: Se clasificó de acuerdo a si no toma o toma. Si toma, se clasificó el consumo diario de acuerdo a menos de una taza, una o dos tazas, o si toma 3 tazas o mas (17).

cigarrillos: Se clasificó de acuerdo a si fumaba, fuma o no fuma (13). Si fuma, se clasificó el consumo diario, semanal o mensual de acuerdo a menos de una cajetilla, una cajetilla o mas de una cajetilla.

Nos interesa conocer, primeramente, el efecto que pueden ejercer los tipos de alimentación sobre la depresión y la ansiedad, pero también conocer cuanto influyen estas otras variables o factores en la variable dependiente.

Con el propósito de obtener un perfil de los hábitos alimentarios de los diferentes grupos, se hizo un análisis del consumo de alimentos de cada grupo. Este análisis se llevó a cabo de la siguiente manera:

1) Se completó un cuestionario donde se registró la frecuencia en el consumo de alimentos de los sujetos.
2) De la data obtenida se realizó un Análisis de Frecuencia de la ingesta de alimentos por grupo. Esto permitió obtener un perfil de los alimentos que ingiere cada grupo con mas frecuencia.
3) Se utilizó un programa de nutrición mecanizado (Your Personal Nutritionist versión 3.2.1) diseñado por Fitzpatrick (18) para registrar los diferentes tipos de alimentos que los sujetos consumen y obtener la composición nutricional de los alimentos que ingiere cada grupo de acuerdo al porciento de requisitos mínimos diarios (MDR). De este programa se obtuvo el contenido nutricional de los alimentos para los siguientes nutrientes: (vitaminas) A, B1, B2, B3, B5, B6, B12, B15, C, D, E, biotina, colina, ácido fólico, inositol y PABA; (minerales) sodio, calcio, fósforo, potasio, magnesio, selenio, iodo, cinc, hierro, manganeso, cobre; (amino ácidos) fenalina/tirosina, leucina, lisina, valina, isoleusina, thereonina, metionina/cistina y triptófano; grasa, proteínas, carbohidratos, calorías totales, calorias de la grasa, colesterol y fibras.
4) Se obtuvo la media y la desviación estándar de cada grupo, para cada nutriente para conocer los niveles nutricionales de cada grupo.
5) Se hizo un análisis de correlación para determinar cuales de estos nutrientes correlacionan con la ansiedad y la depresión.

RESULTADOS

La muestra seleccionada estuvo constituida por 80 sujetos de 25 a 70 años de edad. De estos, el 61% se encontraban entre los 36 y 55 años. El 54% eran hombres y 46% mujeres. La mayoría de los sujetos, el 69%, tenían bachillerato o maestría y el 86% de los participantes estaban empleados. Los ingresos de la muestra fluctuaron entre 200 y 8,000 dolares men-

suales, siendo la mediana $2,443.00. El 51% de la familias estaban constituidas de 1 a 3 miembros y utilizaban $300.00 ó mas para la compra de alimentos.

En cuanto a la salud, el 46% consideraron que su salud era excelente y el 43% que era buena. A pesar de esto, solo el 78% de los sujetos expresaron que no tenían problemas de salud. Del 21% de los sujetos que tenían algún problema de salud, no se pudo establecer un patrón específico de enfermedad. De las 9 condiciones de salud identificadas en la muestra, 3 eran enfermedades degenerativas, tales como hipoglucemia, alta presión y cáncer en las mamas. En general, los sujetos tenían buenos hábitos de temperancia. De los sujetos encuestados, el 69% considera la actividad física que realiza como moderada (un 49%) o mucha (un 20%). Es interesante señalar que, el 79% de los sujetos no hacen uso de bebidas alcohólicas, el 94% no fuma y que solo el 31% hace uso del café de manera moderada (1 a 2 tazas al día).

Con el propósito de conocer si existen diferencias significativas en los niveles de ansiedad y depresión entre los grupos con diferentes tipos de alimentación (vegetariana y omnívora) se realizó un análisis de covarianza. En este análisis se incluyeron los siguientes covariables: sexo, uso de café, cigarrillo y bebidas alcohólicas, y programa regular de ejercicios.

Los resultados del Análisis de Varianza (ANCOVA) indican que las diferencias encontradas en las 3 pruebas psicológicas administradas resultaron significativas. Para la prueba IDARE1, la F=4.697 y el nivel de significancia (ns) fue de 0.005. Para la prueba IDARE2, F=5.088 y el ns=0.003. Para la prueba CES-D, F=4.847 y el ns=0.004. Se encontró que de las covariables analizadas resultaron significativas las variables fumar (P<.003) para la prueba IDARE1 y cafeína (P<.003) para la prueba IDARE2. En el análisis de covarianza se encontró que las covariables contribuyeron a aumentar la varianza explicada de forma significativa. Para IDARE 1, F=3.546 y el ns=0.002. Para IDARE 2, F=2.972 y el ns=0.003. Para la prueba CES-D, F=2.617 y el ns=0.014.

En la Tabla 1 se observan las medias y las desviaciones está ndares para cada una de las pruebas psicológicas administradas.

Observese que el grupo 3 (carnes rojas y otras) y el grupo 4 (carnes blancas y pescado) obtuvieron las puntuaciones mas altas en todas las pruebas. Por el contrario, los grupos que no ingieren carnes, grupo 1 (vegetarianos puros) y grupo 2 (vegetarianos ovolácteos), obtuvieron los niveles de ansiedad y depresión mas bajos. Observese que en las pruebas IDARE1 e IDARE2 la tendencia es progresiva. El grupo 3, que incluye carnes rojas y otras en su alimentación, obtuvo las puntuaciones mas altas en las pruebas. Esto es, una media de 36.80 en IDARE1 y de 36.30 en IDARE2. Le sigue el grupo de carnes blancas y pescado el cual obtuvo una media de 31.20 en IDARE1 y de 31.50 en IDARE2. Por otro lado, los grupos que no utilizaban carnes resultaron con puntuaciones que están por debajo de 31.13 que es la puntuación media del total de sujetos. Puede observarse que el grupo 1 (vegetariano puro), obtuvo una media de 26.25 en IDARE 1 y de 26.55 en IDARE 2 y en el grupo 2 (vegetariano ovolá cteo) las medias en IDARE 1 y 2 fueron 30.25 y 28.75, respectivamente. Observese además que en la prueba CES-D, que mide depresión, los grupos que consumen carnes obtuvieron también las puntuaciones mas altas de esta prueba, a diferencias de los vegetarianos ovolácteos y puros cuyas puntuaciones también están por debajo de la media. Se puede observar además que en la prueba CES-D el grupo 2 (ovolácteo vegetariano) fue el que obtuvo los niveles de ansiedad mas bajos.

Tabla 1
Resumen de promedios y desviaciones estándares por prueba

GRUPOS	IDARE1		IDARE2		CES - D	
	Prom.	**Desv. Std.**	**Prom.**	**Desv. Std.**	**Prom.**	**Desv. Std.**
1	26.2500	4.4824	26.5500	4.8933	6.1000	4.9620
2	30.2500	7.0627	28.7500	5.5619	4.5500	4.1609
3	36.8000	9.2940	36.3000	10.0948	15.8000	10.4257
4	31.2000	9.4957	31.5000	9.4396	9.3500	11.0324
Población Total	**31.1250**	**8.5823**	**30.7750**	**8.5180**	**8.9500**	**9.1857**

Los resultados obtenidos en los análisis de varianza (ANCOVA) nos llevan a aceptar las hipótesis 1 y 2 del estudio. Estas afirman que se observaran diferencias significativas en los niveles de ansiedad y depresión entre los grupos con diferentes tipos de alimentación, sugiriendo que el consumo de carnes pudiera influir en los estados de ansiedad y depresión de los individuos. Los resultados de la prueba ANCOVA nos permiten aceptar en parte la hipótesis 3 del estudio. Esta afirma que la introducción de las covariables contribuye a explicar, en parte, la varianza observada y a reducir la varianza residual. En los análisis de covarianza se encontró que las variables sexo, actividad física, uso de alcohol, fumar y cafeína contribuyen a explicar la varianza enre los grupos. Para la prueba IDARE 1, el nivel de significancia para la varianza explicada fue de 0.002, para la prueba IDARE 2 fue de 0.006 y para la prueba CES-D esta fue de 0.014. Aunque contribuyeron a explicar la varianza entre los grupos se encontró que solo las covariables fumar (con un nivel de significancia de 0.003) y la cafeína (con uno de 0.03) reflejan una relación significativa con los niveles de ansiedad que experimentan los sujetos para las pruebas IDARE1 e IDARE2, respectivamente.

El coeficiente de regresión de la variable fumar en la prueba IDARE1 es 5.458 y para la prueba IDARE2 fue de 4.387. Estos coeficientes nos permiten establecer la dirección en que se da la interacción en estas variables. Esto sugiere que el fumar y tomar café también tienen una asociación directa con los niveles de ansiedad de los sujetos observados en las pruebas IDARE1 e IDARE2.

Se llevó a cabo un análisis de los hábitos alimentarios de los sujetos. Este consistió en registrar todos los alimentos que consumen con mas frecuencia, los sujetos bajo estudio. Esto es, se seleccionaron aquellos alimentos cuya frecuencia era mayor o igual a 3, ya que estos eran los que mostraban mayor consumo. Esto equivale a seleccionar aquellos alimentos que se consumen mas de una vez al mes.

En la Tabla 2 se observan las frecuencias de consumo de cada alimento para los 4 grupos estudiados.

El análisis por inspección de las frecuencias de consumos para los distintos alimentos se expone a continuación tomando en consideración las diferentes agrupaciones de alimentos.

Grupo de leche y sus productos. Se encontró que todos los grupos excepto los vegetarianos puros, hacen uso de productos lá cteos varias veces a la semana. Las leches que mas utilizan son la leche baja en grasa y la leche completa. Estos hacen uso del queso siendo el grupo 3 (carnes rojas y otras) el que obtuvo la frecuencia de consumo de queso mas alta (f=7). Los vegetarianos puros no hacen uso de productos lácteos. Utilizan en su lugar leche y quesos (producidos de semillas y nueces). Además utilizan con menor frecuencia, una vez a la semana (f=3), la leche de soya.

Grupo vegetales. Se puede observar que todos los grupos hacen uso de una variedad de vegetales, aunque se observa una leve disminución en la frecuencia de consumo de algunos vegetales en el grupo 3 (carnes rojas y otras). En general, los vegetales que mas consumen todos los grupos son la lechuga, la zanahoria, el repollo, el brécol y el tomate. Es interesante notar que los vegetarianos puros hacen uso diariamente de germinados, tales como la alfalfa y otros.

Grupo frutas y jugos. En este grupo de alimentos se puede observar que los 4 grupos hacen uso de frutas frescas, frutas cítricas y jugos naturales. Todos hacen uso de las frutas deshidratadas siendo los grupos vegetarianos los que mas frecuentemente la consumen (f=5). Observese, además, que el grupo de vegetarianos puros hace un mayor uso de la papaya y el guineo, mientras que los ovolácteos hacen un mayor uso de las manzanas.

Grupo de cereales y viandas. Observese que todos los grupos, excepto el de carnes rojas y otras, consumen mayormente cereales de grano entero, pan integral, arroz integral, papas y viandas. Por el contrario, el grupo de carnes rojas y otras no ingiere algunos alimentos integrales (como cereales de grano entero y pastas) y consume arroz no-integral, pan blanco y cereales listos para servir. Por otro lado, los vegetarianos puros no ingieren frecuentemente alimentos no-integrales como el pan y cereales listos para servir.

Grupo proteína vegetal. Se observa que todos los grupos hacen uso de los granos de forma moderada, pero los 2 grupos vegetarianos utilizan con mas frecuencia las lentejas (f=4) y nueces (f=6). Los grupos 1 y 2 también hacen uso de productos procesados a base de gluten (f=3) y soya (f=5).

Grupo grasas y condimentos. Todos los grupos utilizan frecuentemente el aceite y condimentos naturales y los demás productos los utilizan de forma moderada. También se puede observar que el grupo vegetariano puro hace uso de otros productos como el aminoácido Bragg y mantequilla de nueces. Observese además que los grupos 3 y 4 (grupos omnívoros) ingieren mayormente pollo y pavo y el grupo que come carnes rojas y otras las come con moderación (f=4).

Grupo azucares y otras misceláneas. Se observa que el grupo 3 (carnes rojas y otras) consume mas azúcar refinada (f=6), bebidas gaseosas (f=6), postres (f=3) y dulces (f=5), seguido por el grupo 4 (carnes blancas y pescado) el cual utiliza mayormente azúcar negra (f=7), postres (f=6) y miel (f=7). Los grupos 1 y 2 (vegetarianos) utilizan con moderación estos productos

Tabla 2
Frecuencias De Consumo De Cada Alimento Por Grupo de Acuerdo a la Escala de Frecuencia

PRODUCTOS	VEGETARIANOS		CARNES	
	PURO	OVOLÁCTEO	ROJAS	BLANCAS
LECHE Y SUS PRODUCTOS				
LECHE	-	5	5	6
LECHE SOYA	-	3	-	-
LECHE DESCREMADA	-	3	4	3
LECHE BAJA EN GRASA	-	4	6	6
MANTECADOS	-	-	4	-
QUESO	-	6	7	5
SOYA	3	3	-	4
YOGUR	-	3	3	4
LECHE SEMILLAS	6	-	-	-
QUESO SEMILLAS	4	-	-	-
VEGETALES				
BERENJENA	3	4	3	4
BRÉCOL	6	6	4	6
ESPINACA	4	4	-	3
GUISANTES DULCES	4	4	3	4
HABICHUELAS TIERNAS	4	4	4	4
LECHUGA	7	7	6	6
MAÍZ	3	5	4	4
REPOLLO	6	6	4	6
TOMATE	5	6	6	5
VEGETALES MIXTOS	5	6	4	4
ZANAHORIA	7	7	5	6
CALABAZA	6	6	3	6
GERMINADOS	7	-	-	-
RÁBANOS	3	-	-	-
PEPINILLOS	-	-	3	-
REMOLACHA	-	-	-	3
FRUTAS O JUGOS				
FRUTAS CÍTRICAS	7	6	7	5
FRUTAS ENLATADAS	-	-	-	-
FRUTAS DESHIDRATADAS	5	5	3	4
OTRAS FRUTAS FRESCAS	7	7	7	6
MANZANA	5	6	3	5
UVA	3	-	3	-
GUINEO	6	4	3	4
PAPAYA	6	-	-	-
KIWI	-	3	-	-
MELÓN	3	3	-	-
PERA	-	3	-	3
FRESAS	-	-	3	-
MANGÓ	3	-	-	-
CRANBERRY	-	3	-	-
HIERBA DE TRIGO	4	-	-	-
PIÑA	3	-	3	-
JUGOS NATURALES	8	8	7	8
JUGOS ENLATADOS	-	4	4	5
NÉCTARES ENLATADOS	-	-	3	3

(Continuación de la tabla 2)

PRODUCTOS	VEGETARIANOS		CARNES	
	PURO	OVOLÁCTEO	ROJAS	BLANCAS
CEREALES Y VIANDAS				
ARROZ	-	5	7	5
ARROZ INTEGRAL	6	6	4	7
CEREAL DE GRANO ENTERO	7	7	-	5
GERMEN DE TRIGO	-	3	-	3
AVENA	5	5	3	5
FARINA	-	3	3	3
HARINA DE MAÍZ	3	5	3	3
VIANDAS	6	6	5	6
PAPAS	6	7	6	6
BATATAS	4	5	5	4
PAN	-	5	7	5
PAN INTEGRAL	7	7	5	7
GALLETAS	-	4	5	3
PASTAS ALIMENTICIAS	4	6	5	4
CEREALES LISTOS	-	5	7	5
PASTAS INTEGRALES	3	-	-	-
PROTEÍNA VEGETAL				
GANDULES	4	3	4	3
GARBANZOS	4	4	4	4
HABICHUELAS ROSADAS	4	6	5	5
HABICHUELAS NEGRAS	3	3	3	3
LENTEJAS	6	4	-	3
PRODUCTOS PROCESADOS A BASE DE GLUTEN	3	4	-	-
PRODUCTOS PROCESADOS A BASE DE SOYA	5	5	-	3
TOFÚ	4	5	3	3
NUECES	7	6	3	3
MANTEQUILLA DE MANÍ	-	4	-	-
HUEVOS	-	4	4	3
GRASAS				
MARGARINA	3	5	5	5
MANTEQUILLA	4	4	4	3
MAYONESA	-	3	4	-
ACEITE	7	7	6	7
MANTECA VEGETAL	-	-	3	-
CONDIMENTOS NATURALES	8	8	7	7
ADOBO, SAZONES	3	4	7	3
ACEITE DE OLIVA	6	4	3	-
AMINOÁCIDO BRAGG	3	-	-	-
MANTEQUILLA DE NUECES	3	-	-	-
CARNES				
CARNE DE RES	-	-	4	-
POLLO	-	-	6	4
PAVO	-	-	6	5
TERNERA	-	-	3	-
JAMÓN	-	-	5	-

(*Continuación de la tabla 2*)

PRODUCTOS	VEGETARIANOS		CARNES	
	PURO	OVOLÁCTEO	ROJAS	BLANCAS
MISCELÁNEOS				
AZÚCAR REFINADA	-	-	6	3
AZÚCAR NEGRA	5	5	3	7
MIEL	7	5	3	5
BEBIDA GASEOSA	-	3	6	3
MALTAS	-	-	3	-
POSTRES	3	3	6	6
GALLETAS DULCES	-	3	4	3
DULCES	3	3	5	3
FRITURAS	-	-	4	-
JALEAS Y MERMELADAS	3	3	3	-
EMPAREDADOS	-	4	4	4
PIZZA	-	3	4	-
POSTRES INTEGRALES	3	3	-	-
ALGAS	3	-	-	-
DULCES INTEGRALES	4	-	-	-

Escala de Frecuencia: 3= una vez a la semana; 4= dos veces a la semana; 5= 3 a 4 veces a la semana; 6= 5 a 7 veces a la semana; 7= una vez al día; 8= más de una vez al día; - menor de una vez al mes

evitando las azucares refinadas, maltas y frituras. Observese que el grupo vegetariano puro evita las azucares refinadas, bebidas gaseosas, maltas, galletas, dulces frituras y pizza.

Se realizó un análisis de correlación para conocer si la ingesta de algunos alimentos por sí solo influyen a los estados de depresión o ansiedad. En la Tabla 3 se presentan aquellos alimentos que correlacionan de forma significativa (nivel de significación 0.01 y 0.001) con las pruebas que miden ansiedad (IDARE1, IDARE2) y depresión(CES-D).

En general, se observa que las correlaciones fluctúan entre 0.29 y 0.42. De acuerdo a Sánchez (19), correlaciones de 0.26 a 0.50 sugieren una asociación moderadamente baja entre las variables. Observese, además, que productos como la pizza, el pan, arroz y los cereales listos para servir relacionan positivo con algunas de las pruebas que miden ansiedad o depresión. Observese que las carnes también muestran tener asociación con la ansiedad y la depresión. Se puede observar que algunos alimentos como la miel, las nueces, la lechuga y el brécol demuestran tener una asociación inversa con algunas de las pruebas, esto es, a mayor frecuencia de consumo de estos productos en la dieta mas bajos los resultados de las pruebas, o sea, menos indicadores de ansiedad o depresión en los sujetos. Estos resultados confirman la hipótesis H5, la cual afirma que algunos alimentos como la carne, las harinas y los azucares influyen en los niveles de ansiedad o depresión. Observese que algunas carnes como la de res, hígado y pollo correlacionan directamente con los indicadores de ansiedad y depresión. Observese que otros alimentos como las harinas procesadas, el arroz, el pan, los cereales listos para servir, galletas y dulces reflejan una asociación positiva con las pruebas que miden ansiedad o depresión. Además, los productos como cereales integrales, el brécol, al lechuga, las nueces y la miel correlacionan inversamente con la ansiedad y la depresión.

Con el propósito de obtener los niveles nutricionales de cada grupo bajo estudio, se utilizó el programa nutricional computadorizado. Los análisis nutricionales obtenidos para cada sujeto se analizaron estadísticamente para obtener las medias y las desviaciones estándares para los 4 grupos bajo estudio.

En este análisis, los 4 grupos obtuvieron porcientos por encima de los especificados por el MDR, para gran parte de los nutrientes. Los grupos vegetarianos puros y vegetarianos ovolá cteos obtuvieron niveles mucho mas altos que los sujetos que consumen carnes en los nutrientes como el hierro, vitaminas A, B1, B6, E, C, cinc, manganeso y ácido fólico. Por otro lado, en el grupo 1 (vegetarianos puros) se observan niveles por debajo del MDR en las vitaminas B5, B12, y calcio entre otros. Por otro lado, los 4 grupos obtuvieron niveles adecuados de los 8 aminoácidos esenciales. Se encontró que el porciento de calorías como producto de grasas y proteínas en los vegetarianos es comparable

Tabla 3
Correlación de Alimentos con Pruebas

Correlaciones	Idare1	Idare2	CES- D
Queso	0.3070 *	———	———
Brécol	———	———	- 0.3564 **
Habichuela	———	0.2963 *	———
Lechuga	———	———	- 0.3053 *
Arroz blanco	0.3343 *	———	———
Cereales integrales	- 0.2961 *	———	———
Cereales listos para servir	———	0.3118 *	———
Pan	0.3349 *	———	0.3752 **
Nueces	———	———	- 0.3210 *
Mayonesa	0.3673 **	0.2975 *	0.3888 **
Mantequilla vegetal	0.3877 **	0.4064 **	0.3479 *
Adobos	0.2750 *	———	———
Carne de res	0.4182 **	0.3469 *	0.3930 **
Higado	0.2887 *	0.3278 *	———
Pollo	———	———	0.3563 **
Miel	- 0.3157 *	———	- 0.3248 *
Galletas dulces	———	———	0.2996 *
Jaleas	———	0.3028 *	———
Pizza	———	0.2890 *	0.3794 **
Jamón	0.2884 *	———	———

1-TAIL SIGNIF: *-0.01 **0.001

con la de los omnívoros, aunque el porciento de calorías por concepto de carbohidratos es mucho mas alto en los grupos vegetarianos. Al comparar los 4 grupos se encontró que el grupo con mayor consumo en calorías es el grupo 3 (carnes rojas y otras), seguido por los dos grupos vegetarianos. El grupo que menos cantidad de calorías consume es el grupo 4 (carnes blancas y pescado).

A pesar de este patrón, el grupo vegetariano puro es el que menos cantidad de colesterol ingiere en su alimentación, seguido por el grupo ovolácteo vegetariano, siendo el que mas colesterol ingiere el grupo carnes rojas y otras. Por último, se pudo observar un patrón en cuanto a la ingesta de fibra. Los grupos vegetarianos son los que consumen la mayor cantidad de fibra, aunque los 4 grupos consumen una cantidad razonable de fibra en su dieta.

CONCLUSIONES

Los resultados de este estudio ofrecen evidencia de que existe una posible relación entre la ingesta de carnes y otros alimentos, y los niveles de ansiedad y depresión que experimentaron los sujetos bajo estudio. Este es, si no el primero, uno de los pocos estudios que sostienen esta relación. Los resultados sugieren además una posible relación entre el fumar o tomar café y los niveles de ansiedad observados en los sujetos.

En el presente estudio los resultados de los análisis dietarios sostienen los hallazgos de la literatura científica. Se encontró que las dietas vegetarianas son altas en carbohidratos complejos y fibra, y bajas en colesterol. También se evidenció que son altas en antioxidantes como las vitaminas A (caroteno), C y E. En los análisis dietarios realizados también se encontró que la alimentación vegetariana pura contiene cantidades adecuadas de proteínas y hierro, pero son deficientes en vitaminas B12, calcio, zinc, y bajas en colesterol.

Por otro lado, se encontró que los grupos omnívoros obtuvieron niveles adecuados de todos estos nutrientes, excepto zinc donde apuntaron por debajo de los grupos vegetarianos. Este es un dato interesante que arrojó el presente estudio. Las deficiencias en zinc son un problema de salud pública que están tomando en consideración muchos países en desarrollo (20). El mineral zinc es esencial en la nutrición porque contribuye a una diversidad de funciones dentro del desarrollo y mantenimiento del organismo. Según la evidencia científica, el zinc contribuye a muchos procesos del cuerpo, incluyendo el sistema inmunológico, el cual ayuda a regular las células blancas, contribuyendo a proteger la célula de daño debido a los radicales libres (21). Se ha estudiado, especialmente, la deficiencia de este mineral con relación a la perdida de gusto, olor y apetito en poblaciones de envejecientes (22,23). También, se han encontrado deficiencias

de zinc en pacientes de cáncer en la prostata. En el área de las condiciones mentales, se han encontrado deficiencias de éste mineral en casos de depresión, esquizofrenia y otras condiciones relacionadas al sistema nervioso central (24). Estos datos podrían tener implicaciones en el área de la salud pública en Puerto Rico si se corroboran las deficiencias de este mineral en grupos de poblaciones puertorriqueñas, como pacientes con cáncer de la prostata y en relación a enfermedades degenerativas donde está envuelto el sistema inmunológico.

Según los hallazgos expuestos, los vegetarianos utilizan alimentos con un contenido mas alto de carbohidratos complejos. En el análisis dietario realizado en el presente estudio no se encontró relación entre los niveles nutricionales (basados en el MDR) y los indicadores de ansiedad y depresión que experimentaron los sujetos. En general, se encontró que los cuatro grupos tenían niveles adecuados de ácido fólico, vitamina B6, vitamina C y hierro. Todos los grupos bajo estudio tenían niveles de zinc por debajo de lo esperado. Por otro lado los niveles de vitamina B12 en los grupos vegetarianos estaban por debajo de los especificados por los MDR. Los vegetarianos puros tenían niveles muy bajos de colesterol ingerido (5.5 gramos).

Cabe señalar que en el análisis de correlación no se encontraron correlaciones significativas entre los niveles nutricionales y los estados de ansiedad y depresión. Por el contrario, solo se encontró relación moderadamente baja y positiva en los niveles de colesterol y vitamina B12 para la prueba IDARE2, esto es, correlaciones moderadamente bajas de 0.3315 y 0.3097, respectivamente. Esto sugiere que los niveles bajos de colesterol y vitamina B12 en estos sujetos, están asociados con puntuaciones bajas en la prueba IDARE2, lo cual indica niveles bajos de ansiedad.

Otro aspecto a señalar es que a diferencia de los nutrientes, se observa mayores correlaciones entre los alimentos que ingieren los sujetos y los estados de ansiedad y depresión que estos experimentaban (vease Tabla 3). Es interesante señalar además que dentro de las correlaciónes mas alta se encontraron la carne de res y la de pollo. Esto nos lleva a confirmar en base a los hallazgos que el consumo de carnes pudiera influir en los estados de ansiedad o depresión de los individuos estudiados.

De acuerdo a los resultados encontrados en este estudio, sugerimos a aquellas personas que padecen de ansiedad o depresión que consideren como alternativa mejorar sus hábitos alimentarios como pueden ser el reducir o eliminar la ingesta de carnes y grasa saturadas, y aumentar el consumo de carbohidratos complejos, granos, frutas y vegetales. Al momento de planificar su alimentación, estos deben tomar en consideración el consultar a un nutricionista u otros profesionales de la salud para asegurarse de suplir al organismo con los niveles adecuados de los nutrientes esenciales, especialmente las vitaminas, minerales y aminoácidos esenciales.

Antes de concluir, queremos señalar que durante el proceso de entrevista, algunos vegetarianos comentaron sobre el aumento en sensibilidad (elemento subjetivo) que han experimentado luego de iniciarse en este tipo de alimentación. Sensibilidad ante situaciones que ocurren en el medio ambiente, como por ejemplo, ante el dolor ajeno, los logros personales y otros, lo cual ha contribuido a mejorar su calidad de vida. Debemos, pues, fomentar mayor investigación en esta área con adecuada metodologia, ya que la dieta y su manejo pueden ser un factor importante, no solamente en la prevención de enfermedades físicas, sino también mentales (25).

Abstract: *The following study, one of the first done in Puerto Rico, investigate the different kinds of diet and the level of anxiety and depression that the subjects present. The sample consists of 80 subjects between 25 and 70 years age divided into two main groups (vegetarian versus no vegetarian) depending their diet consumption. The basic findings in the three psychological tests given (IDARE-1, IDARE-2 and CES-D) to the subjects demostrate significant differences in anxiety and depression between groups. More anxiety and depression where reported in the no vegetarian groups in comparison with the vegetarian groups. In addition, diet analysis found more nutritional antioxidant agents levels in the vegetarian group in comparison with the no-vegetarian group.*

Key Words: Puerto Ricans, diet, anxiety, depression

REFERENCIAS

1. Kuzma JW: Adventists and Good Health. **Adventists Review Seminar.** 1989; 166: 15-19.

2. Ornish D, Brown SE, Scherwitz LW et al: Can lifestyles changes reverse coronary heart disease?. Medical Science. **THE LANCET.** 1990; 336: 129-133

3. Silverberg D.: Non-Pharmacological treatment of hypertension. **Journal of Hypertension.** 1990; 8: (suppl.4), S21 S26.

4. Phillips, RL, Snowdon, DA y Brin, BN: Cancer in vegetarians. **Environmental Aspects of Cancer - The Role of Macro and Micro Components of Foods.** Westport, Food and Nutrition Press, 1983: 53-72.

5. Kestin M, Rouse IL, Correll RA, Nestel PJ: Cardiovascular disease risk factors in free-living

men: Comparison of two prudent diets, one based on lactoovovegetarianism and the other allowing lean meat. **American Journal of Clinical Nutrition.** 1989; 50: 280-287.

6. Millet P, Guilland JC, Fuchs F, Klepping J: Nutrient intake and vitamin status of healthy French vegetarians and nonvegetarians. **American Journal of Clinical Nutrition.** 1989; 50: (4), 718-727.

7. Nieman DC, Underwood BC, Sherman KM et al: Hematological, anthropometric, and metabolic comparisons between vegetarian and nonvegetarian elderly women. **International Journal of Sport Medicine.** 1989; 10: (4), 243-251.

8. Nieman DC, Underwood BC, Sherman KM et al: Dietary status of Seventh Day Adventist vegetarian and nonvegetarian elderly women. **Journal of the American Dietetic Association.** 1989; 89: (12), 1763-1769.

9. Brants HA, Löwik MR, Westenbrink S, Hullshof KF, Kistemaker C: Adequacy of a vegetarian diet at old age (Dutch Nutrition Surveillance System). **Journal of the American College of Nutrition.** 1990; 9: (4), 292-3.

10. Kuzma, JW, Lindsted KD: Determinants of Eight-Year Diet Recall Ability. **Journal of Clinical Epidemiology.** 1990; 1: (5), 386-391.

11. Harland BF, Smith SA, Howard MP, Ellis R, Smith JC: Nutritional status and phytate: zinc and phytate x calcium: zinc dietary molar ratios of lacto-ovo vegetarian Trappist monks: 10 years later. **Journal of the American Dietetic Association.** 1989; 88: (12), 1562-1566.

12. O'Connell JM, Dibley MJ, Sierra J, Wallace B, Marks JS, Yip R: Growth of vegetarian children. The Farm Study. **Pediatrics.** 1989; 84: (3), 475-481.

13. Löwik MR, Schrijver J, Odink J, van den Berg H, Wedel M: Long-Term effects of a Vegetarian Diet on the Nutritional Status of Elderly People (Dutch Nutrition Surveillance_System). **Journal of the American College of Nutrition.** 1990; 9: (6), 600-609.

14. Papalia, DE, Olds, SW: **Desarrollo humano.** Méjico: Ultragráfica. 1985.

15. Kurzweil P: Daily Values Encourage Healthy Diet. FDA Consumer Special Report: "Focus on Food Labeling". Department of Health and Human Services. **Penn State Nutrition Center.** PA, 1993; Doc. Num. 12101988.

16. Ullmann, D, Phillips, RL, Beeson, WL et al: Cause-specific mortality among physicians with differing life-styles. **JAMA,** 1991; 265: (18), 2352-2359.

17. Kuzma, JW, Lindsted KD, Anderson, JL: Coffee Consumption and Cause Specific Mortality. **Journal of Clinical Epidemiology.** 1992; 45: (7), 733-742.

18. Fitzpatrick, B: **Your Personal Nutritionist Versión 3.2.1.** P.O. Box 282. Veneta. Oregon. 97487. 1991.

19. Sánchez Viera, J: **Fundamentos del razonamiento estadístico.** Santo Domingo, República Dominicana, Editora Corripio. 1992.

20. Sanstead, HH: Is zinc deficiency a public health problem? **Nutrition.** 1995; 11: 87-92.

21. Black, RE: Conference on Zinc for Child Health. **John Hopkins School of Higiene and Public Health.** Maryland, Baltimore, November, 1996.

22. Hall, K: Orthomolecular Therapy: Review of the Literature. **Orthomolecular Psychiatry.** 1975; 4: (4), 297-313.

23. Mertz, W: **Trace Elements in Human and Nutrition.** 5th Ed. New York, Academic Press Inc, 1986; 2: 1-137.

24. Pfeiffer, C: **Nutrition and Mental Illness.** Vermont, Rochester, Healing Arts Press, 1987.

25. Rodríguez, J, González, MJ: Hacia una visión médica futurista: Nutrición y Dietoterapia preventiva. **Hospitales.** 1990; 28: 9-11.

Vol. 90 • 4 - 5 - 6 / 1998 • Pág. 69, 73

Estudios Originales:

Gastroschisis: a ten year review

Victor N. Ortiz MD. FACS. FAAP *; David H.Villarreal MD. *; José González Olmo MD. FAAP **; Carlos Ramos Perea MD. FAAP **

Summary: *From 1983 to 1993, 30 cases of gastrochisis were managed at the Mayaguez Medical Center. Ninety percent of these patients underwent primary closure of their abdominal wall defect. Three of 30 patientes (10%) required silastic or goretex silos with final closure in an average of 8 days. There was no sex predilection, the average birth weight was 2.4 kg and the mean gestional age was 36 weeks. Thirty percent had associated anomalies, the majority were intestinal artresia, and/or undescended testicles. Twenty one (70%) of infants were delivered vaginally. Nine children (30%) were delivered via cesarean section. Four cesarean sections were done solely after prenatal ultrasonic identification of gastroschisis. There was no improvement in hospital stay, complications, or days until enteral feeds were tolerated when vaginally delivered patients were compared to those born by c-sections. In seven patients mesh sheeting (Marlex) was used for closure of late hernia defects. The mean hospital stay was 50 days and the mean time to enteral feedings 20 days.*

All patients required postoperative mechanical ventilation for an average of 4 days. There was no mortality. Our data and review of the literature do not support gastroschisis prenatal diagnosis as a sole indication for cesarean section. Our data showed favorable prognosis for most babies. Primary fascial closure can be accomplished safely in the majority of patients.

No single operative strategy is ideal for all patients, and treatment of individual defects should be tailored to the degree of visceroabdominal disproportion.

INTRODUCTION

Gastroschisis is a congenital defect of the periumbilical body wall through which abdominal contents protude. The eviscerated organs are not covered by skin, amnion, or peritoneal membranes. Although the embryologic distinction between gastroschisis and omphalocele remains controversial, (1,2,3) the differentiation is clinically useful. When compared to patients with omphalocele, infants with gastroschisis less frequently have other life-threatening anomalies and are virtually always candidates for definitive operative treatment. However, gastroschisis patients are more subject to prolonged ileus because of prolonged exposure of the bowel to amniotic fluid during gestation, with resulting edema of the entire intestinal wall.

In 1943, Watkins reported the first successful reduction of a gastroschisis in the United States with primary fascial closure.(4). Prior to the development of adequate mechanical ventilation for neonates, primary closure was considered hazardous due to respiratory and vascular compromise from elevated intra-abdominal pressure. In an attempt to delay reduction and still provide coverage of the viscera, Gross reported a method of skin flap coverage of three large omphaloceles in 1948,(5). The mortality diminished even though infants were left with large ventral hernias, which needed later repair . Skin flap coverage was frequently used for the next 20 years,(6).

As with other congenital anomalies, the survival of infants with gastroschisis dramatically improved in the late 1960's. Neonatal intensive care, particularly mechanical ventilation and parenteral nutrition, was instrumental in increasing the salvage of these infants. Coincident with these advances in postoperative management was the introduction of staged reduction of abdominal wall defects using prosthetic material. Shusterís landmark paper of 1967 reported the progressive reduction of eleven omphaloceles using a "keel" or "reef" of teflon mesh, (7). His technique was modified by Allen and Wren in 1969,who fashioned the prosthetic material into a "Silo" or "chimney" and accomplished reduction by milking the prosthetic tube downward every 1 to 3 days,(8). Because of the current alterations in management, it remains unclear whether the marked decreased in mortality that has occurred is due to application of the silo annex or to general improvements in supportive care of these neonates.

The choice of fascial closure, skin coverage, or placement of a silo still depends on the surgeon's subjective assesement of the abdominal wall tension during attempted reduction. This leads to considerable variation in the treatment of gastroschisis, (9,10,11). Other authors feel that primary closure is infrequently possible and that a prosthetic annex should be used in virtually all cases, (11,12).

All correspondence should be addressed to: Dr. Victor N. Ortiz - Box 3008 Mayaguez, PR 00681
*From the Department of Surgery * and Pediatrics ** - Mayaguez Medical Center, Mayaguez, Puerto Rico*

Still others contend that prosthetic material poses an unwarranted risk of sepsis and that most patients with gastroschisis should be treated with skin flap coverage,(13). There has also been recent recognition that the present sophisticated management of ventilation and other aspects of perioperative care allows many of these infants to safely undergo a "snug" primary closure,(14). We present a review of our clinical experience during a ten year period with the surgical management of gastroschisis and compare our results with the most pertinent literature on the subject.

MATERIALS AND METHODS

The charts of 30 patients treated for gastroschisis at the Mayaguez Medical Center from January 1, 1983 through December 31, 1993 were reviewed with regard to sex, birth weight, gestational age, length of hospital stay, mode of delivery, prenatal diagnosis, use of hyperalimentation , need for a stoma, type of repair (primary vs. silo), use of mesh for closure of hernia complications, anomalies, viscera outside the abdomen, days until enteral feedings were tolerated, days on mechanical ventilation and mortality.

RESULTS

There was no sex predilection (16 male, 14 female). The average birth weight was 2.4 kg and the mean gestational age 36 weeks. The average maternal age was 18.2 years and 50% of all mothers were primiparous. In the 12 cases where it had been noted on the chart, the mother underwent a prenatal ultrasound examination sometime during pregnancy and in four the presence of an abdominal wall defect was noted. Twenty-one of 30 children were delivered vaginally.

TABLE 1:
Children born via cesarean with gastroschisis as an indication Versus overall.

	CESAREAN FOR GASTROSCHISIS	OVERALL
# of patients	4	30
Mean birth wt.	2.48 kg	2.40 kg
Mean gestational age	37.0 wks	36.0 wks
Central venous access	4/4 (100%)	30/30 (100%)
Arterial monitoring	3/4 (100%)	20/30 (66.6%)
Stoma	0/4 (0%)	3/30 (10%)
Primary repair	3/4 (75%)	27/30 (90%)
Silo	0/4 (0%)	3/30 (10%)
Mesh need	1/4 (25%)	7/30 (23.3%)
Average days to oral feedings	18 days	20 days
# of days intubated	4 days	4 days
# of complications	50%	50%
Hospital stay	47 days	50 days
Mortality	0	0

Four cesarean sections were performed solely for prenatal ultrasonic identification of gastroschisis. The perinatal data, morbidity and mortality of this group was compared with the overall experience as shown in table 1.

The presence of viscera and types were noted. Small bowel was found outside of the abdominal cavity in all patients, large bowel in 27 of 30 (90%), stomach in 18 of 30 (60%). In three patients the herniated stomach was greater than half its size, and all these required silo construction (fig. 1). Tubes and/or ovaries were identified in 6 cases (20%), testicles in 4 (13%), bladder in 2 (7%), and liver in one patient.



Fig.1. Gastroschisis with large portion of the stomach herniated

Nine children were born with 12 other anomalies in addition to their gastroschisis. Of these 12 defects there were 5 undescended testicles, 2 bowel atresias, 1 volvulus, 2 cardiac anomalies, 1 cleft palate and 1 phocomelia. (fig. 2) There was no reported family history of abdominal wall defects in any of the patients reviewed.

Twenty-seven children underwent primary closure of their abdominal wall defect at the time of initial operation. Three required construction of a silo when bowel contents could not be safely reduced after manual dilatation of the abdominal wall and expulsion of most of the meconium. The average time spent in silo removal and secondary closure was 8 days (fig. 3a, 3b, 3c). No gastrostomies were performed. Three patients needed stomas secondary to intestinal atresia or volvulus. No primary anastomosis were performed. The average duration of intubation was 4 days and all patients required endotracheal intubation and respiratory support. All children required central total parenteral nutrition, without use of the umbilical vein.

The total number of patients with complications was 15 (50%). The average overall time until feedings



Fig.2. Gastroschisis with volvulus and phocomelia

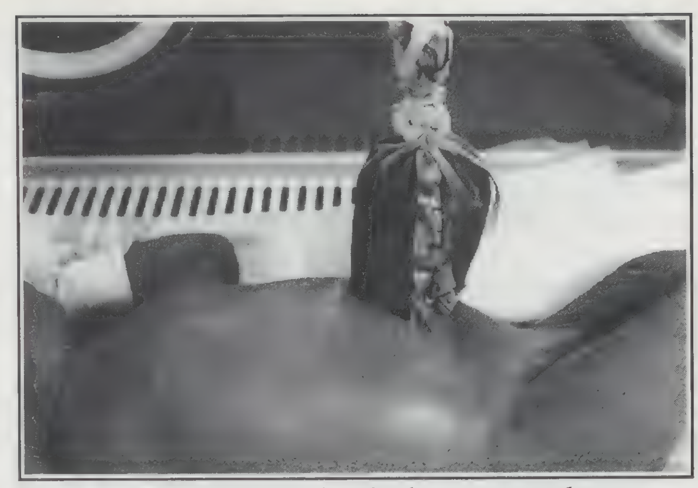


Fig.3A. Gastroschisis treated with silo 1st post-op day

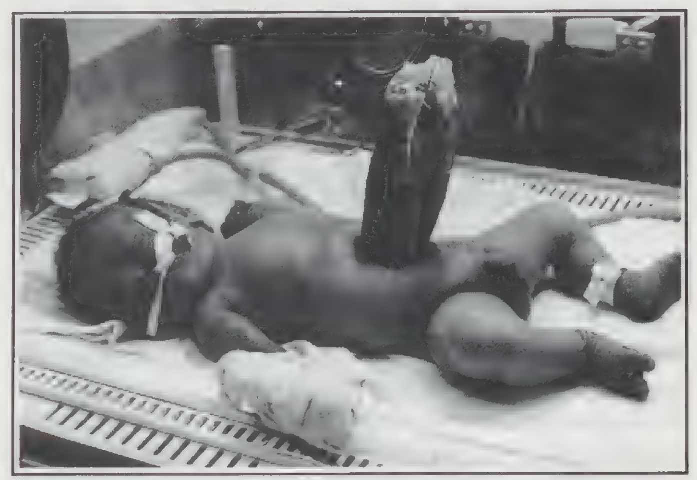


Fig.3B. Gastroschisis treated with silo 3rd post-op day

TABLE 2:
Treatment of patients with gastroschisis.

Total # of cases	30
Primary repair	27/30 (90%)
Silos	3/30 (10%)
Days until closed (Silos)	8
Stomas	3/30 (10%)
Gastrostomies	0
Central venous lines	30/30 (100%)
Mechanical ventilation	30/30 (100%)
Average days intubated	4



Fig.3C. Gastroschisis treated with silo 7th post-op day

were tolerated was 20 days. The average hospital stay was 50 days. There was no mortality

DISCUSSION

Experience demonstrates that children born with gastroschisis have few associated anomalies and in general do well. We found a 30% malformation rate which is compatible with that found in other reviews, (15,16) Indeed, these data suggest that aggressive nutritional support, ventilatory management, and close monitoring improve the outcome of these children. This is reflected in fewer complications, shortened time until enteral feedings are tolerated, and decreased length of hospital stay as seen by others.(15,17,18)

TABLE 3:
Complications

Total no. of patients	30
Total no. of patients with complications	15 (50%)
Total no. of complications	20
Pneumatosis/NEC	1
Wound breakdown	2
Small bowel obstruction	0
Gangrenous bowel	0
Reflux	4
Short gut syndrome	1
Sac sepsis	1
Enterocutaneous fistula	0
Seizures	2
Ventral hernia	7
Intra ventricular bleed	0
Aspiration pneumonia	2

As was stated by Dilorenzo et al, primary closure should be done when possible,(15) Our rate of primary closure was better than the 82.5% of that particular survey. But, as pointed out by Bryant et al,(17) vigorous attempts at primary closure may reduce respiratory function and jeopardize intestinal viability. In these cases the surgeonís experience is of outmost importance. He might switch to a silo technique or mesh the defect. When more than 50% of the stomach is edematous and the small intestine is also included in the whole edematous process, some authors use intravesical pressure monitoring to decide if primary abdominal closure should be performed or not. However, in our experience results have been erratic, and we have continued to base our decision for primary closure mostly on the percentage of stomach and small bowel edema present.

There was no mortality, which we feel reflects our team aggressive use of hyperalimentation , ventilatory support and successful selective use of primary versus silo closure and to the proper use of Marlex sheeting when required.

Elective cesarean section has been advocated by some when the prenatal diagnosis of gastroschisis has been made by ultrasound, (19).

Others have shown that perinatal injury and mortality does not support this practice.20,21,22,23 Although our data is small it showed that babies delivered by cesarean section fare no better than the group as a whole with respect to days intubated, complications, number of surgical procedures, hospital stay, days until enteral feedings were tolerated and mortality. Prenatally diagnosed gastroschisis cannot be considered a sole indication for cesarean section, at least based on our oven experience.

Resumen: *Desde el 1983 al 1993, 30 casos con gastroschisis fueron manejados en el Centro Médico de Mayaguez. Noventa por ciento de estos defectos abdominales se cerraron primariamente. Diez por ciento requirieron silos de goretex y/o silástico temporales, llevandose a cabo el cierre final en aproximadamente 8 dias. No hubo ningun tipo de diferencia respecto al sexo, siendo el peso promedio al nacer de 2.4 kg y la edad gestacional promedio de 36 semanas. Treinta por ciento tuvieron anomalias asociadas,la mayoria de estas, atresia intestinal, vólvulo y/o testículos no-descendidos. Setenta por ciento de los infantes nacieron vaginalmente y nueve nacieron por cesárea. Cuatro de estas nueve cesareas se llevaron a cabo con el propósito de manejar la gastrosquisis previamente identificadas. No hubo diferencia en tiempo de estadía, complicaciones o dias transcurridos hasta lograr tolerar dieta por boca entre el grupo diagnosticado prenatalmente y el grupo en general. En siete pacientes se utilizo malla de marlex para el cierre final de pequeñas hernias incisionales.*

El promedio de estadia hospitalaria fue de 50 dias y el tiempo promedio en tolerar dieta por boca fue de 20 dias. Todos los pacientes requirieron intubacion endotraqueal posoperatoria para un promedio de 4 dias.

No hubo mortalidad. Nuestros datos y repaso de la literatura no apoyan el hecho de que la gastroschisis diagnosticada prenatalmente sea la única indicación para llevar a cabo una cesárea. Nuestros datos demuestran que el pronóstico en gastrosquisis es excelente y que un cierre primario del defecto se puede llevar a cabo en la mayoría de los casos. Sin embargo no hay una estrategia terapéutica superior a otra y el manejo inicial debe ser individualizado dependiendo del grado de desproporción viscero-abdominal del paciente.

BIBLIOGRAPHY

1. DeVries P.A. The pathogenesis of gastoschisis and omphalocele J. Ped Surg. 1973 15: 245-251.

2. Duhamel B. Embriology of exomphalos and allied malformations Arch Dis Child. 1963 38: 142-147.

3. Shaw A. The myth of gastoschisis J. Ped Surg. 1975 10:235-244.

4. Watkins D.E. Gastroschisis with case report Virginia Medical Monthly. 1943 78:42-44.

5. Gross R.E. A new method for surgical treatment of large omphaloceles. 1948 24:277-292.

6. Moore T.C., Stokes G.E. Gastroschisis Surgery. 1953 33:112- 120.

7. Schuster S.R. A new method for the staged repair of large omphaloceles Surg Gyn Obst. 1967 12:837-850.

8. Allen R.G., Wren E. Jr. Silon as a sac in the treatment of omphalocele and gastrschisis J. Ped Surg. 1969 4:3-8.

9. Ein S.H., Rubin S. Z. Gastroschisis: primary closure or silon pouch J. Ped Surg. 1980 15:549-552.

10. Fonkalsrud E.W. Selective repair of neonatal gastroschisis based on degree of visceroabdominal disproportion Ann Surg. 1980 191:139-144.

11. King D.R., Savrin R., Boles E.T. Jr. Gastroschisis update. J. Ped Surg. 1980 15:553-557.

12. Schwwartz M. Z., Tyson K.R., Milliorn K., Lobe T.E., Staged reduction using a silastic sac is the treatment of choice for large congenital abdominal wall defects J Ped Surg. 1983 18:713-717.

13. Thompson J., Fonkalsrud E.W. Reappraisal of skin flap closure for neonatal gastroschisis Arch Surg. 1976 111:684-687.

14. Canty T.G., Collins D.L. Primary facial closure in infants with gastroschisis and omphalocele: a superior approach J Ped Surg. 1983 18:707-712.

15. DiLorenzo M., Yazbeck S., Ducharme J.C. Gastroschisis: A 15 year experience J. Ped Surg. 1987 22:710-712.

16. Mayer T., Blak R., Matlack M.E. Gastroschisis and omphalocele. An eight year review Ann Surg. 1980 192:783-787.

17. Bryant M.S., Tepas J.J. III, Mollit D.L. The effect of initial operative repair on the recovery of intestinal function in gastroschisis Am Surg. 1989 55:209-211.

18. Blane C.E., Wesley J.R., DiPietro M.A. Gastrointestinal complications of gastroschisis Am J. of Roentgenol. 1985 144:589-591.

19. Lenke R.R., Hatch E.L. Fetal gastoschisis: A preliminary report advocating the use of cesarean section Obstet Gynecol. 1986 67:395-398.

20. Bond S.J., Harrison M.R., Filly R.A. Severity of intestinal damage in gastroschisis. Correlation with prenatal sonographic findings J. Ped Surg. 1988 23:520-525.

21. Carpenter M.W., Curci M.R., Dibbins A.W. Perinatal management of ventral wall defects Obstet Gynecol. 1984 64:646-651.

22. Kirk E.P., Wah R.W. Obstetric management of the fetus with omphalocele or gastroschisis: A review and report of one hundred twelve cases Am J. Ostet Guynecol. 1983 146:512-518.

23. Mercer S., Mercer B., DíAlton M.B. Gastroschisis: Ultrasonographic diagnosis, perinatal embriology, surgical and obstetric treatment outcomes Can J. Surg. 1988 31:25-26.

Estudios Originales:

Pediatric Thyroid Nodules: Insights in Management

*Humberto Lugo-Vicente, MD, FACS, FAAP *,*
*Víctor N. Ortíz, MD, FACS, FAAP ***

Abstract

Background: *Multiple diagnostic studies are utilized to unveil malignancy in pediatric thyroid nodules and determine whether surgical therapy is needed.*

Purpose: *The aim of this report was to determine whether management of pediatric thyroid nodules has changed with the current use of diagnostic modalities such as ultrasonography (US), radionuclear scans (RNS) and fine needle aspiration biopsy (FNAB).*

Material/Methods: *Twenty-four children with thyroid nodules managed during a ten-year period comprised the study group. Demographic characteristics, clinical manifestations, US and RNS imaging findings, FNAB results, surgical therapy, complications and pathological reports were retrospectively reviewed. US, RNS and FNAB results were categorized as either benign, malignant, suspicious or insufficient.*

Results: *Females outnumbered males by a five to one ratio. Mean age was 14.9 years. Nineteen nodules were benign (79%) and five malignant (21%). All children were euthyroid. Benign nodules were soft, movable, solitary and non-tender. Malignant nodules were characterized by localized tenderness, a multiglandular appearance, and fixation to adjacent tissues. US and RNS gave no clue toward management since cystic and hot nodules figured among malignant cases respectively. US achieved 86% accuracy, 80% sensitivity and 88% specificity; RNS showed 26% accuracy, 80% sensitivity and 11% specificity; FNAB achieved 80% accuracy, 60% sensitivity and 90% specificity. Suppressive thyroid hormone therapy was useless in the few cases tried. Physical examination findings, persistence of the nodule, progressive growth and cosmetic appearance where the most common indications for surgery.*

Conclusions: *Present diagnostic modalities played a minor role in the decision to withhold surgery. US was useful for aiming aspiration of cystic nodules. RNS decided the functionality of the nodule, but its accuracy was far from ideal. FNAB is a safe procedure whose greatest help was to resolve in case of suspicious or malignant cytology that a more radical procedure is needed. Clinical judgement as determined by serial physical findings and suspicion continues to be the most determinant factors in the management of thyroid nodules in children.*

Index words: *thyroid nodules, ultrasound, radio-nuclear scans, fine needle aspiration biopsy*

Thyroid nodules affect a small percent (1-2%) of the pediatric population at large [1-2-3], Long term clinical institutional reviews are needed to accumulate sufficient number of cases and produce meaningful results. Main concern is that thyroid carcinoma can be identified in 14 to 40% of asymptomatic solitary thyroid nodules in children[2], The need to differentiate malignant from benign lesions is the most challenging predicament in management[1]. The ideal goal is to identify and surgically excise malignant nodules while avoiding a neck procedure in children with benign nodules. Unfortunately present diagnostic work-up is unreliable in achieving this goal.

Present diagnostic work-up consists of ultrasonography (US), radionuclear scans (RNS) and the use of fine-needle aspiration biopsy (FNAB) cytology. Recent renewed interest has tocused FNAB as the ultimate diagnostic test to decide whether a thyroid nodule should be removed or observed[4,5]. There are scattered reports in children with thyroid nodules managed solely from FNAB cytology. Drawbacks of FNAB such as age, neck size, cyto-pathological expertise, amount of specimen obtained, the need for heavy sedation or anesthesia for the procedure has made this approach unpopular for pediatric patients. We questioned whether ultimate surgical excision for histologic confirmation will be needed in most cases of pediatric thyroid nodules in the current era of diagnostic modalities.

Within this report we review our experience with 24 children with thyroid nodules managed during the last ten-years at two major University- based Hospitals in Puerto Rico.

MATERIALS and METHODS

Our study population consisted of twenty-four children with thyroid nodules managed in the Pediatric Surgery Departments of the University

*From the section of Pediatric Surgery, Department of Surgery, UPR School of Medicine and the University Pediatric Hospital, Medical Science Campus, Rio Piedras, PR.
**Section of Pediatric Surgery, Department of Surgery, Mayaguez Medical Center, Mayaguez, PR.
Address reprints to: **Humberto Lugo Vicente, MD-** P.O. Box 10426, Caparra Heights Station, San Juan, PR 00922-0426. E-mail: titolugo@coqui.net

Pediatric Hospital (Rio Piedras, PR) and Mayaguez Medical Center (Mayaguez, PR) from January 1985 to June 1995. Retrospective medical chart analysis was achieved. Demographic characteristics, clinical manifestations (history and physical examination), thyroid function tests, diagnostic imaging results (radionuclide scans and ultrasonography), FNAB results, surgical therapy, complications and pathological reports were obtained from the charts, tabulated and analyzed.

US findings in twenty-two children were categorized as either solid, cystic or complex. For purpose of analysis solid and complex findings were classified as suspicious of malignancy, and cystic characteristics as benign findings. RNS findings in twenty-three patients were categorized as cold, warm or hot. Cold and warm RNS findings were registered as suspicious of malignancy and hot findings as benign. FNAB results in eighteen patients were classified as either benign, malignant, suspicious or insufficient[4]. FNAB results reported with follicular cells were categorized as benign, instead of categorizing them as suspicious of malignancy as described by others[6].

US, RNS and FNAB reports were compared with the final histologic diagnosis in each case. Each result was then classified as either **true-positive** (malignant or suspicious from a nodule found histologically malignant), **true-negative** (benign from a nodule found histologically benign), **false positive** (malignant or suspicious from a nodule found with benign histology) or **false-negative** (benign from a nodule found with malignant histology). The accuracy, specificity, and sensitivity were determined for each diagnostic test as previously reported in the literature[5]. Independent clinical risk factors differentiating children with benign and malignant pathology were assessed for each group.

Analysis of the data was rendered using EPI-lnfo v 6.04 Statistical package (CDC, Atlanta). A probability less than 0.05 was considered statistically significant. Results are expressed as mean ± standard deviation unless otherwise stated. Specific tests included chi-square, student-t test and analysis of variance (ANOVA).

Technique of FNAB

Most of these aspirates were done by a pathologist using a 22-gauge needle attached to a 10 cc syringe manually or using a mechanical aspiration device. Two to five separate aspirates were done. Smears done are placed in 95% ethanol fixative in preparation for Papanicolaou stain or air dried to be stained with modified Wright stain (Diff Qwik). If there were more than seven groups of cells per stain smear was sufficient. Criterias are similar to those used by the Armed Forces Institute of Pathology[4,7].

RESULTS

Twenty-four children underwent surgical treatment for a thyroid nodule; ten (42%) came from Mayaguez Medical Center and fourteen (58%) from the University Pediatric Hospital. Females outnumbered males by a five to one ratio. Most cases occurred during mid-adolescence (mean age 14.9 years with a range of nine to 18). One-third had familiar history of goiter. None received ionizing irradiation to the neck or presented history of goitrogen ingestion. Nineteen nodules were benign (79%) and five malignant (21 %) by histologic requirements.

All children were euthyroid. Fifteen had nodules in the right lobe, twelve in the left, six bilateral, and one central in location. Most children presented a soft, non-tender, movable, non-fixed solitary nodule, 25% had a multinodular goiter, 17% palpable lymphadenopathy, 13% a nodule fixed to adjacent tissue, and one child (4%) had hoarseness. Benign nodules were movable ($p = 0.007$), soft ($p = 0.03$), non-tender ($p = 0.04$), and solitary ($p = 0.01$). Conversely, malignant nodules showed localized tenderness ($p = 0.04$), a multiglandular appearance ($p = 0.04$), and fixation to adjacent tissues ($p = 0.04$).

Diagnostic imaging studies comprised twenty-two ultrasounds (US) and twenty-three pertechnetate ^{99m}Tc radionuclear scans (RNS). US findings uncovered thirteen solid (59%), seven cystic (32%), and two complex (9%) masses. Four malignant nodules had solid characteristics, and one had predominantly cystic findings on US. The accuracy rate of US was 86%, sensitivity 80%, and specificity 88%.

Scintigraphic studies identified nineteen cold (83%), three hot (13%), and one warm (4%) nodule. Of five malignant nodules, three were cold, one hot and one warm. Both hot and warm nodules were managed with thyroid hormone (synthroid) suppressive therapy with no change in size. The diagnostic accuracy of RNS was 26%, sensitivity 80% and specificity 11%. Comparison of FNAB with final histology is shown in Table 1. Eleven (61 %) were read as benign,

Table 1:
FNA cytology and histologic diagnosis in 18 pts.

FNA cytology	No	(%)	Histology Benign (13)	Malignant (5)
Benign	11	(61)	9	2
Malignant	2	(11)	0	2
Suspicious	2	(11)	1	1
Indetermine	3	(17)	3	0

No in ( ) are %

two (11 %) malignant, two (11 %) suspicious, and three insufficient (17%). Two cases of papillary carcinomas showed psammomas bodies in the FNAB. Of seven cytologic samples read with follicular cells six were follicular adenoma and one colloid nodular goiter. Six children without FNAB testing were younger (mean age 13.8 years), had cold nodules on scanning, four were solid and two complex, and the main indication for surgery was progressive growth along with clinical characteristics. The final score-box of each diagnostic modality (accuracy, sensitivity and specificity) can be appreciated in Table 2.

Table 2:
Score box of diagnostic modality

	No pts.	Sensitivity	Specificity	Accuracy
Ultrasound	22	80%	88%	86%
Radionuclear Scan	23	80%	11%	26%
FNAB	18	60%	90%	80%

Surgery was needed to establish a diagnosis of benign or malignant pathology in most cases. Benign pathology was managed with lobectomy and isthmectomy in sixteen children and subtotal thyroidectomy in three cases with multinodular goiter. Malignant nodules underwent total thyroidectomy, three with excision of central lymph node compartment, and one with ipsilateral modified radical neck dissection. Eight cases suffered surgery- related complications: four transient episodes of hypocalcemia, three with transient hoarseness, and one wound keloid formation. Complications were more commonly encountered in total thyroidectomy cases (p = 0.03). No patient had permanent hypoparathyroidism or vocal cord paralysis, and there was no mortality.

Pathological findings are depicted in Table 3. Patients were follow-up for a mean of 516 days. Papillary carcinomas predominated in four children with multiglandular involvement in two cases. Children with carcinoma and positive lymph node metastasis received adjuvant radioactive therapy and are free of disease 1, 1.5 and 4.5 years respectively. The mixed carcinoma was diagnosed after careful examination showed signs of angio-invasion.

Multiple analysis of risk factors showed that children with malignant nodules were older, with characteristic physical exam findings (multiglandular appearance, localized tenderness, fixed to adjacent tissue), had more time with symptoms, and developed more complications due to the extent of surgery (Table 4).

Table 3:
Pathologic Findings

Benign	**19 (79)**	
Follicular adenoma		13
Colloid Nodular Goiter		3
Lymphocytic thyroiditis (Hashimoto)		2
Hürthle cell adenoma		1
Malignant	**5 (21)**	
Papillary		4
Mixed		1

No in ( ) are %

Table 4:
Risk factors by multivariate analysis

	Malignant (5)	Benign (19)	P
Age (years)	16.4	14.5	0.03*
Time with symptoms (wk)	235	56	NSS
Physical Characteristics			
Tendergroth	3	3	0.04*
Multiglandular	3	3	0.04*
Fixed to adjacent tissue	2	1	0.04*
Surgery related complications	4	4	0.03*

*p< 0.05, NSS = not statiscally significant

DISCUSSION

Previous pediatric series have reported a significant incidence of malignant thyroid nodules that has leveled to 20 to 30% [8,9]. This drop is the result of eliminating needless radiation to the head and neck area during early childhood[10]. Other high risk factors associated with malignancy are females in pubescence, goitrogen consume, endemic area, and history of familial thyroid illness[3,10]. Nine children in our study group (38%) had familial history of thyroid disease. Familial thyroid ailments may now represent a larger proportion of childhood nodules[10].

History and physical examination has been an integral tool in deciding the surgical management of thyroid nodules with help from nuclear scans, ultrasonographic studies and FNAB[1,11,12]. Most investigators agree that surgical extirpative therapy is needed to establish a final histologic diagnosis and accomplish a cure in the significant number of cases with malignancy[1,13]. Clinical characteristics of malignancy are rapid growth, palpable cervical nodes, recurrent laryngeal nerve dysfunction, transient localized tenderness, pressure on surrounding

structures, and attachment to overlying tissue[9,11]. Our children with malignant nodules were characterized by a multiglandular appearance, localized tenderness, and fixation to adjacent tissues. Localized tenderness represents an acute bleeding episode inside a solid tumor with necrosis and cyst formation[8,11].

US and scintigraphic studies have been extensively used as diagnostic methods of determining whether the imaging characteristics of the nodule suggest malignancy. Solid or complex appearance on US, and cold or warm RNS uptake are regarded as characteristic of malignancy[12,14]. In our series of patient both studies (US and RNS) were of limited utility since malignancy was recognized among cystic and hot nodules. Both studies served to detect patients with developmental errors in thyroid development (i.e., lingual and pre-hyodal thyroid, agenesis of one lobe or superior extension of the isthmus of the gland)[15]. Ultrasound can enable an accurate aspiration to be done under direct vision[16]. Scintigraphy further defines the functional status of the nodule correlating with thyroid function tests to determine whether a hot nodule should be managed with antithyroid suppressive medication or surgery. Most hot nodules will not shrink with thyroid hormone therapy and frequently enlarge during prolonged follow-up[17]. Surgical therapy in autonomous functioning thyroid nodules may be needed with thyrotoxic symptoms, progressive growth, or the suspicion of malignancy[3,17,18].

FNAB has emerged as the most sensitive screening tool to limit the number of thyroid resections in the adult population[19,20,21]. Cited drawbacks to its use in the pediatric age are those related to the sampling method, the proficiency of the aspirator, the experience of the cytopathologist, and the trouble in differentiating benign Hürthle cells and follicular tumors from their malignant analogues[20]. FNAB has not been extensively employed in children due to age, neck size, cytopathological expertise, amount of specimen obtained, the need of heavy sedation or anesthesia for the procedure, and the possibility of complications[22]. The 80% accuracy rate of FNAB in our series is far from the ideal rate reported in the literature[21]. FNAB did not reduce the number of patient undergoing thyroidectomy in our present study. Its best role was to help decide whether a more aggressive gland removal was needed in those cases found suspicious or frankly malignant. We, like other investigators, believe that benign FNAB findings should be viewed with cautiousness and should have close clinical follow-up[5]. FNAB is a diagnostic test that needs the interpretation of the clinician and with clinical findings of malignancy the child should undergo surgery[21].

US was found a more accurate and sensitive test than FNAB. The probability (sensitivity) that a malignant thyroid nodule had suspiciously or frankly malignant cytology was 60% and 80% on FNAB and US respectively; the probability (specificity) that a benign thyroid nodule had negative cytologic findings on FNAB and US were 90% and 88% respectively in our series. The low sensitivity of FNAB places the test in doubt, and the high specificity is the result of a higher number of patients with cytological findings of follicular cells in the aspirate. No attempt was made to differentiate follicular adenoma from follicular carcinoma since capsular and vascular invasion cannot be adequately assessed by FNAB aspiration alone. Follicular adenoma continues to be the most common benign pathological finding in children[23]. The high numbers of cases with follicular adenoma giving cytopathological results in FNAB that cannot exclude follicular carcinoma were the main reason for surgical therapy. RNS was the least specific and sensitive of the three diagnostic tests used.

Children with malignant thyroid nodules were generally asymptomatic and euthyroid[9]. Multiple analysis identified several independent risk factors. Those harboring malignant thyroid nodules are usually females in their late teens, have characteristic physical findings already discussed, maintain symptoms for an extended period and upon surgical therapy suffer more complications. The complications of thyroid surgery are proportional to the extent of gland removal and disease process[24]. Suppressive thyroid hormone therapy is useless in the management of thyroid nodules and what it does is increase the time with symptoms[25]. Indications for surgery in our group of children consisted of nodular clinical characteristics, evidence of increase in size, cosmetic appearance and FNAB findings.

Our study illustrates that most pediatric thyroid nodules are benign and surgery will be needed to exclude malignancy in the actual era of multiple diagnostic modalities. Physical examination findings, persistence of the nodule and progressive growth are main indications for surgery. Thyroid function tests, scintigram and ultrasounds have limited usefulness in differentiating benign from malignant nodules[11,26]. FNAB is a safe procedure playing a minor role in our decision to withhold surgery. Its helped to anticipate in case of malignancy that a more radical procedure was needed. Clinical judgement and suspicion remain the most important determinants in management.

Resumen

Trasfondo: *Múltiple estudios diagnósticos se utilizan para investigar las características de los nódulos del tiroide en la edad pediátrica y determinar la necesidad de tratamiento quirúrgico.*

Propósito: *El propósito de este estudio era determinar si*

el manejo de los nó dulos del tiroides en niños ha variado en la era actual de estudios diagnó sticos como la ultrasonografía (US), las pruebas radio-nucleares (RNS), y la biopsia de aspiración de aguja fina (FNAB).
Materiales/Métodos: *Veinticuatro niños con nódulos en el tiroide manejados durante un lapso de diez años fueron objeto de estudio. Las características demográ ficas, manifestaciones clínicas, resultados de imágenes y FNAB, terapia quirúrgica, complicaciones y reportes patológicos fueron evaluados retrospectivamente. Los resultados de US, RNS y FNAB fueron categorizados como benignos, malignos, sospechosos de malignidad e indeterminados.*
Resultados: *La proporción de hembras a varones fué de cinco a uno. La edad promedio 14.9 años. Diecinueve nódulos resultaron benignos (79%) y cinco malignos (21%). Todos los niños estaban normo-tiroideos. A la palpación los nódulos benignos eran suave, movibles, solitarios e indoloros. Lo nódulos malignos se caracterizaron por dolor localizado, una apariencia multiglandular y fijos al tejido adyacente. El US y las pruebas RNS no ayudaron al manejo toda vez que nódulos quísticos y calientes figuraron entre los casos malignos respectivamente. El US adquirió una certeza de 86%, una sensitividad de 80% y especificidad de 88%; los estudios RNS fueron certeros 26%, sensitivos 80% y específicos 11%. La FNAB obtuvo una certeza de 80%, una sensitividad de 60% y una especificidad de 90%. Terapia hormonal de supresión fue inútil en los pocos casos que se utilizó. Los hallazgos del examen físico, la persistencia del nódulo, su crecimiento progresivo y la apariencia cosméticas fueron las principales razones para optar por cirugía en la mayoría de los casos.*
Conclusiones: *Las actuales pruebas diagnosticas juegan un papel mínimo en la decisión de evitar la cirugía. El US es de ayuda en la aspiración directa de quistes en el tiroide. El estudio RNS puede decidir la funcionalidad del nódulo, pero su certeza en determinar malignidad es muy baja. La FNAB es una prueba segura en la edad pediátrica cuya ayuda principal es decidir en casos de sospecha o franca malignidad que un procedimiento quirúrgico radical será necesario. El juicio clínico, el examen físico seriado y la sospecha de malignidad son los factores mas determinantes en el manejo actual de nódulos del tiroide en niños.*

REFERENCES

1- Hung W, August GP, Randolph JG, et al: Solitary Thyroid Nodules in Children and Adolescents. J Pediatr Surg 17(3): 225-229, 1982
2- Telander RL, Zimmerman D, Kaufman BH, et al: Pediatric Endocrine Surgery. Surg Clinics of North Amer 65(6): 1551-1587, 1985
3- Hung W: Nodular Thyroid Disease and Thyroid Carcinoma. Pediatr Ann 21(1): 50-57, 1992
4- Raab SS, Silverman IF, Elsheikh TM, Thomas PA, Wakely PE: Pediatric Thyroid Nodules: Disease Demo-graphics and Clinical Management as Determined by Fine Needle Aspiration Biopsy. Pediatrics 95(1); 46-49, 1995
5- Degnan BM, McClellan DR, Francis GL: An Analysis of Fine-Needle Aspiration Biopsy of the Thyroid in Children and Adolescents. J Pediatr Surg 31(7): 903-907, 1996
6- Agrawal S: Diagnostic Accuracy and Role of Fine Needle Aspiration Cytology in Management of Thyroid Nodules. J Surg Oncology 58: 168-172, 1995
7- Silverman JF, Frable WJ: The use of Diff-Ouik stain in the immediate interpretation of fine-needle aspiartion biopsies. Diagn Cytopathol 6: 366- 369, 1990
8- Scott MD, Rawford JD: Solitary Thyroid Nodule in Childhood: Is the Incidence of Thyroid Carcinoma Declining? Pediatrics 58(4): 521-526, 1976
9- Silverman SH, Nussbaum M, Rausen AR: Thyroid Nodules in Children: A Ten Year Experience at One Institution. The Mount Sinai Journal of Medicine 46(5): 460-463, 1979
10- Fowler CL, Pokorny WJ, Harberg FJ: Thyroid Nodules in Children: Current Profile of a Changing Disease. Southern Med J 82(12): 1472-1478, 1989
11- Hung W, Anderson KD, Chandra RS, Kapur SP, Patterson K, Randolph JG, August GP: Solitary Thyroid Nodules in 71 Children and Adolescent. J Pediatr Surg 27(11): 1407-1409, 1992
12- Rogers DG: Thyroid Disease in Children. Am Fa Physic 50(2): 344-350, 1994
13- Desjardins JG, Khan AH, Montupet P, et al: Management of Thyroid Nodules in Children: A 20 Year Experience. J Pediatr Surg 22(8): 736-739, 1987
14- 16- Alter CA, Moshang T: Diagnostic Dilemma: The Goiter. Pediatr Clinic North America. 38 (3): 567-578, 1991
15- Schneider: Sonographic Imaging of the Thyroid in Children. Prog Pediatr Surg 26: 1-14, 1991
16- Watters DA, Ahuja AT, Evans RM, Chick W, King MWK, Li AKC: Role of Ultrasound in the Management of Thyroid Nodules. Amer J Surg 164: 654-657, 1992
17- Osburne RC, Goren EN, Bybee DE, et al: Autonomous thyroid nodules in adolescents: Clinical characteristics and results of TRH testing. Journal of Pediatr 100(3): 383-386, 1982
18- Croom IIIRD, Thomas CG, Reddick RL, et al: Autonomously Functioning Thyroid Nodules in Childhood and Adolescence. Surgery 102: 1101-1108, 1987
19- Ng EH, Tan KL, Nambiar R: Impact of Fine Needle Aspiration Cytology on the Management of Solitary Thyroid Nodules. Aust N Z J Surg 60: 463-466, 1990
20- Meko JB, Norton JA: Large cystic/solid thyroid nodules: A potential false-negative fine-needle aspiration. Surgery 118(6): 996-1004, 1995
21- Piromalli D, Martelli G, Del Prato I, Collini P, Pilotti S: The Role of Fine Needle Aspiration in the Diagnosis of Thyroid Nodules: Analysis of 795 Consecutive Cases. J Surg Oncology 50: 247-250, 1992
22- Geiger JD, Thompson NW: Thyroid Tumors in Children. Oto Clin N A August 1996
23- Festen C, Otten BJ, van de Kaa CA: Follicular Adenoma of the Thyroid Gland in Children. Eur I Pediatr Surg 5:262-264, 1993
24- Shaha A, Jaffe BM: Complications of thyroid surgery performed by residents. Surgery 104(6): 1109-1114, 1988
25- Gharib H, James FM, Charboneau JW, Naessens JM, Offord KP, Gorman CA: Suppressive Therapy With Levothyroxine For Solitary Thyroid Nodules: A Double-Blind Controlled Study. N Engl J Med 317(2): 70-75, 1987
26- Garcia CJ, Daneman A, Thormer P, Daneman D: Sonography of Multinodular Thyroid Gland in Children and Adolescent. AJDC 146: 811 -816, 1992

Estudios Originales:

Primitive Peripheral Neuroectodermal Tumors Mayagüez Medical Center Experience

*Juan I . Camps MD. Victor N. Ortiz MD. FACS. FAAP.**
*Oscar Trujillo MD.***

Summary: *Primitive neuroectodermal or neuroepithelial tumors are names used to describe neoplasias composed of undifferentiated cells resembling germinal cells of the embryonic neural tube. These tumors are small round cell malignancies of the neural crest origin arising outside the central and sympathetic nervous system. They are described as peripheral and central neuroectodermal tumors related to the original malignant cell. A great number of tumors are described under this classification in spite of the fact that there is no an universal acceptance that these small-cell neoplasms, regardless of their primary site, are derived from inmature neuroectoderm tissue. Because one tumor resembles others in terms of its phenotypic expresion, multiple specific studies such as clinical profile, ultrastructural, immunocytochemical, and cytogenetic features should be studied, since no single clinical or laboratory marker is by itself diagnostic. However, there is a chromosomal reciprocal translocation, t(11;22)(q24;q12), which is unique to Primitive Neuroectodermal Tumor (PNET).*

INTRODUCTION

The purpose of this study is to present our experience with the PNET at the Mayagüez Medical Center, from 1988 to 1997. After a thorough review of all malignant solid tumors in children, 11 cases were found suggestive of neuroectodermal tumors. All biopsy blocks were sent to the Armed Forces Institute of Pathology for further studies such as Eosin-Hematoxilin, PAS, Trichrome and Immunoperoxidase methods for LCA, S-100, Leu-7, Keratin and Desmin.

Localization of the PNET are as variable as their cell progenitors, the neural crest. It takes different names as Askin's tumors when the tumor is classified as malignant small-cell tumor of Thoracopulmonar origin, Ewing's Sarcoma or Osseal PNET, and others. (Table1)

TABLE 1:
CLASSIFICATION OF THE PERIPHERAL NEUROECTODERMAL TUMORS

Classical Neuroblastoma
Peripheral Neuroepithelioma
Askin's Tumor (Thoracopulmonar)
Ewing's Sarcoma
Pigmented Neuroectodermal Tumor
Intraosseous Neuroectodermal Tumor
Peripheral Medulloepithelioma

PATIENTS AND METHODS

The subject of this review are eleven patients with primitive neuroectodermal tumors treated at the Mayagüez Medical Center from 1988 to 1997. All cases presented were either seen initially at our clinic or referred from other hospitals.

The pathological diagnosis of all suspected PNET cases seen at our center was confirmed by the Armed Forces Institute of Pathologhy. At our medical center the histological criteria for diagnosis by light microscopy were the following caracteristics: fairly uniform and poorly differentiated round cells arranged in cords, nests, or clusters, plus occasional pseudorosettes without dendritic cytoplasmic projections. Periodic Acid-Schiff staining absent, or if present, sparse and diastase resistant. The Ewing 's Sarcoma, despite of its characteristic positive reaction to PAS is included in this study because most articles classify this kind of tumor as osseal PNET.

The study population consisted of 11 young patients managed in the General Surgery Department at the Mayagüez Medical Center from 1988 to 1997. Retrospective analysis of all medical charts was performed. Demographics characteristics, clinical manifestations,

** General Surgery Department, Mayagüez Medical Center. Mayagüez, PR.*
*** Pathology Department, Mayagüez Medical Center. Mayaguez, PR.*
Address correspondence: Victor N. Ortiz MD. PO BOX 3008, Mayagüez. PR.

diagnostic imaging results, histological diagnosis and surgical therapy were obtained from the charts. Ten were males (83%) and two females (17%) for a five to one ratio.(Table 2). Mean age was 8.9 years with a range of 2 months to 24 years. No family history of malignant tumor was found. The most common tumor localization was in the retroperitoneal space [7 cases (58%)], other areas of localization were: pelvis [3 cases (25%)], chest [one case (8%)], and limbs [one case (8%)]. Physical examination findings were those of a huge intraabdominal mass in most of the cases; other physical findings were non-contributory. The size of the tumor was variable from a 2 cm. intraspinal extradural tumor, to a huge unresectable tumor of the retroperitoneum. In some cases the patients died without further treatment. Two cases (17%) required adjuvant chemotherapy after surgical excision.

TABLE 2:
CLINICAL PROFILE

Sex: F-1 M-10	
Age: From 2 months to 19 years	
Race: Hispanic	
Primary site:	Chest: 1.
	Pelvis: 2.
	Retroperitoneal: 7.
	Limbs: 1.
Type of tumor:	Neuroblastoma: 4.
	Ewing's Sarcoma: 3.
	Germ cell tumor: 1.
	Undifferentiated: 1

RESULTS

Clinical Profile: Patient characteristics are summarized in Table 2 Clinical Profile. Most patients were males (9-1) and had localized disease but mostly unresectable. The size of the tumor was variable, from a little tumor of 2 cm of intraspinal extradural tissue at L-5, to a huge unresectable tumor of retroperitoneum. In some cases the patients died witout any more treatment (2 cases), others were sent to The Pediatric University Hospital for adjuvant chemotherapy.

Our cases were described in a population that ranged from infants to young adults with a clear predominance of males. The predominant localization is in the retroperitoneum and the main hystological type is the Neuroblastoma tumor. Distant spread metastasis were found in the liver, bones and lymph nodes groups outside of the primary tumor. Our managment was in all cases a surgical procedure to attempt complete excision when possible and when not possible debulking and or biopsy. At present none of the patients studied are alive.

DISCUSSION

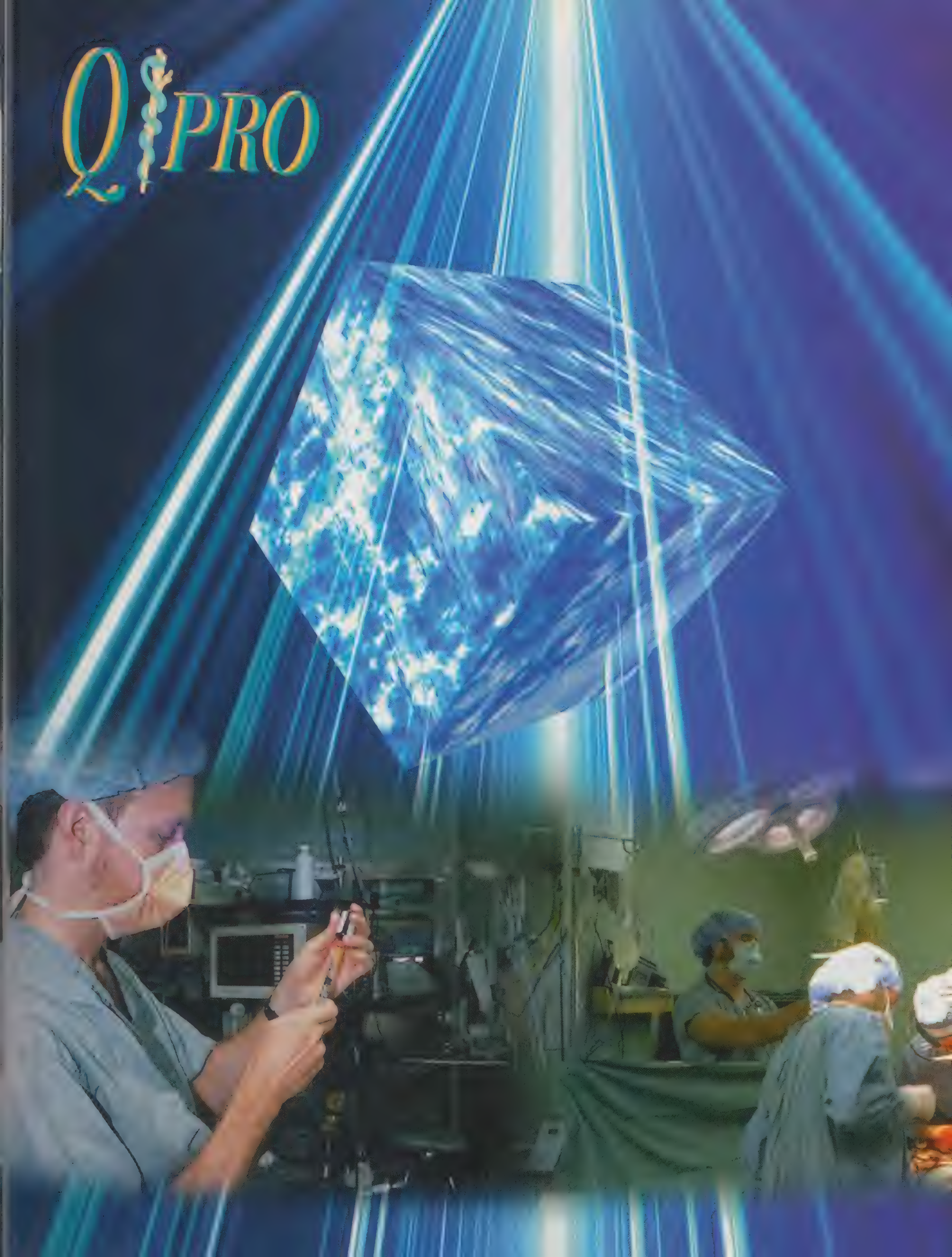
This retrospective study reveals the incidence and prognosis of the PNET in our comunity. These tumors have a very low incidence in the general population. Localization is variable, such as retroperitoneum[1], extremities[2], genitourinary[3], bone[2] and neural tissue[4].

A great number of tumors are described under this classification in spite of the fact that there is no universal acceptance that these small-cell neoplasms are derived from inmature neuroectoderm tissue[5]. These small-cell neoplasms, regardless of their primary site, are derived from inmature neuroectoderm and are histogenetically related. These neoplasms share a number of phenotypic characteristics at the level of morphology, cytogenetics, and immunohistochemistry. Immunohistochemistry has facilitated our ability to differentiate the various PNET from the other non-neural small-cell tumors of childhood such as malignant lymphoma and rhabdomyosarcoma[6,7] Elevated Neuro-specific enolase (NSE) in the serum or cerebrospinal fluid may document the presence of neuroepitheal origin of the neoplasm[8] . The S100 protein has proved to be present in either neural and non neural tissues[9].

The prognosis of PNET is poor and agrees with many other reports[10]. All patients with distant metastasis at diagnosis died of or with disease. In our experince, all patients were found with terminal or advanced disease. In cases of tumors in stage 1 or 2 the treatment is surgical excision. (< 5cm. diameter). In more advanced cases the treatment may be combined with other therapies. The wide variations in type and dose of chemotherapy given to patients with advanced disease of PNET precludes firm conclusions about individual drug efficacy and dose intensity[11]. Radiation therapy can shrink PNET, suggesting radiosensitivity, but this modality does not appear to be curative[12].

In our experience, the diagnosis of the disease in our population was late because patients had no symptoms until the evidence of secondary consequences of the malignancy appeared such as severe weight loss, abnormal palpable masses, etc. Therefore the prognosis in all cases was poor.

In conclusion, the most appropiate PNET therapy might involve a surgical excision of the tumor. Intensive use of chemotherapy active against PNET and radiation therapy to ablate residual microscopic disease, might improve the probabilities of curing the patient, when compared with surgery alone, but adequate primary resection continues to be the most important treatment modality.


QPRO

Resumen: *El tumor neuroectodérmico periférico es un cancer incomún que se localiza fuera del sistema nervioso central. Este grupo engloba a un número de tumores que se caracteriza por estar constituídas de células redondas y pequeñas con origen en la cresta neuronal con específicas diferencias inmunohistoquímicas. Predominan en el grupo poblacional infantil y adolescente. El pobre pronóstico se basa en el avanzado estadío cuando estos tumores son diagnosticados. Este es un estudio retrospectivo de 11 pacientes pediátricos y adultos jóvenes tratados en el Departamento de Cirugía del Centro Médico de Mayagüez.*

REFERENCES

1. Brian H. Kushner, Steven I. Hajdu, Subhash C. Gulati et al. Extracraneal primitive neuroectodermal tumors. The Memorial Sloan-Kettering Cancer Center Experience. Cancer 1991;Vol 67 (April) :1825-29.

2. Louis P. Dehner. Primitive neuroectodermal tumor and Ewing's Sarcoma. Am J Surg Pathol 1993; 17(1):1-13.

3. Narmada P. Gupta, Barinder Pal Singh, V. Raina et al. Primitive neuroectodermal kidney tumors: 2 case report and review of the literature. The Journal of Urology 1995; Vol. 153:1890-2.

4. Michael Noel and Kenneth M. Earle. Primitive neuroectodermal tumors of the brain in children. Cancer 1973;Vol 32: 890-7.

5. Louis P. Dehner. Peripheral and central primitive neuroectodermal tumors. A nosologic concept seeking a consensus. Arch Pathol Lab Med 1986; Vol 110,997-5.

6. TsokosM, Linnoila RI, Chandra RS, et al. Neuron-specific enolase in the diagnosis of neuroblastoma and other small, round cell tumors in children. Hum Pathol 1984; 15: 575-584.

7. Triche TJ, Askin FB, Kissane JM. Neuroblastoma, Ewing's Sarcoma and the differential diagnosis of small, round, blue cell tumor. Major Probl Pathol 1986; 1S:145-195.

8. Dhillon AP, Rode J. Leathem A. Neuron-specific enolase. An aid to the diagnosis of melanoma and neuroblastoma. Histopathology 1982; 6:81-92.

9. Weiss SW, Langloss JM, Enzinger FM. Value of S-100 in the diagnosis of soft tissue tumors with particular reference to bening and malignant Schwann's cell tumors. Lab Invest 1983;49:299-308.

10. Schmidt D, Harms D, Burdach S. Malignant peripheral neuroectodermal tumors of childhood and adolescence. Virchows Arch(a)1985:406:351-365.

11. Watts RG, Castleberry RL, Berkow RL et al. Treatment of peripheral primitive neuroectodermal tumors (PNET) of childhood with combination chemotherapy (Abstr). Proc Am Soc Oncol 1989;8:304.

12. Helson L,. Gulati S, Langleben A et al. Surgery, radiotheraphy and autologous marrow for neuroectodermal tumors (Abstr). Proc Am Soc Clin Oncol 1983;2:79.

SOLICITUD DE AMIGOS PARA LA ADQUISICION DEL CRISTO DE ZURBARÁN

Nombre____

Compañía____

Dirección____

_______________________________Zip_______________

Teléfonos: casa________________Trabajo_______________

( ) Cofradía del Cristo de Zurbarán ($50)

( ) Club de Zurbarán ($1,000)

Incluyo $____

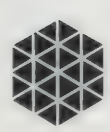
pagadero al Museo de Arte de Ponce

( ) Cheque o giro ( ) Master Card ( ) Visa ( ) Amex

Número de tarjeta_____________________________________

Fecha de vencimiento__________________________________

Firma____



Museo de Arte de Ponce

Apartado 366108

San Juan, P.R. 00936-6108

Tel. 793-4040, Fax. 792-4740

Reporte de Casos:

Uretero-Arterial Fistula: A case report and review of the literature

Juan I. Camps MD., Victor N. Ortiz MD. FACS. FAAP. Jose Vargas MD., Mario Figueroa MD.*

Summary: *We report the case of a uretero-arterial fistula (UAF) formation in a 68 years old male who had previously undergone an Aortobifemoral graft. He got complicated with occlusion and infection of the right lower extremity requiring a right hip disarticulation for its managment. This was followed by groin infection and graft protusion, managed by transabdominal resection of the right graft limb, at which time the right ureter was lacerated and repaired. Several months later, he presented with gross hematuria found to be secondary to UAF. The diagnostic and managment steps leading to this patient care will be reviewed, together with a review of the literature pertinent to this case report.*

KEY WORDS: Uretero-arterial fistula

CASE REPORT:

A 68 year-old male patient was admitted to our institution through the emergency room with a right groin infection due to an infected graft. The patient had a history of peripheral vascular disease related to smoking and high blood pressure. He had a previous aortobifemoral graft followed by a right hip disarticulatioon with stump skin grafting. After admission, and since he had good blood supply to the left lower extremity, the patient underwent exploratory celiotomy and the right leg of the graft removed up to a point, 2 cm. distal to the graft bifurcation. During the dissection, the right ureter was lacerated and repaired over a double J catheter. He was discharged 33 days later with negative blood and urine cultures to be followed in the Urology and Surgery outpatient clinics.

On May 25, 1996, the patient was readmitted with the diagnosis of gross hematuria and symptomatic anemia, several urological diagnostic procedures were performed. An intravenous pyelogram revealed adequate excretion of the contrast on both kidneys and ureters with hydronephrosis of the right side. A cystoscopy revealed bloody discharge from the right ureteral orifice. A right retrograde pyelogram showed contrast spillage at the middle third of the right ureter with local defects suggesting blood contents. (figure 1). A transaxillary aortogram was performed preoperatively revealing leakage of the contrast material from the right side of the graft (figure 2-3). The final diagnosis was of UAF. He was taken to the operating room the next day.

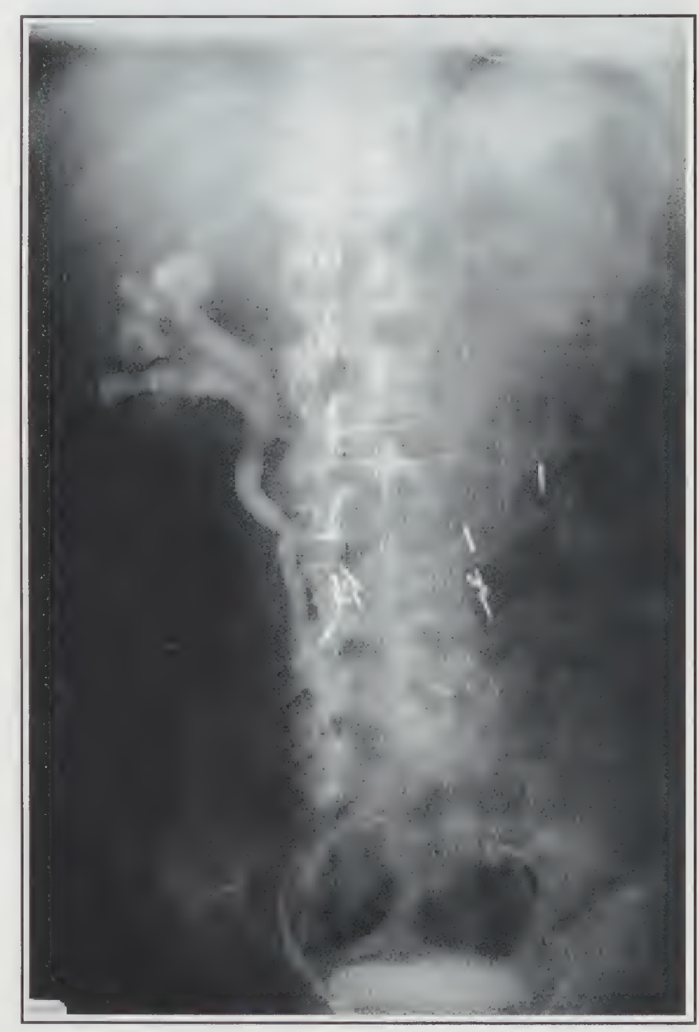


Figure 1: Retrograde pielogram shows a poor define contrast in the middle third level of the ureter.

From the General Surgery Department, Mayaguez Medical Center. Mayaguez. PR
**All correspondence with: Victor N. Ortiz MD, PO BOX 3008. Mayaguez, PR.*

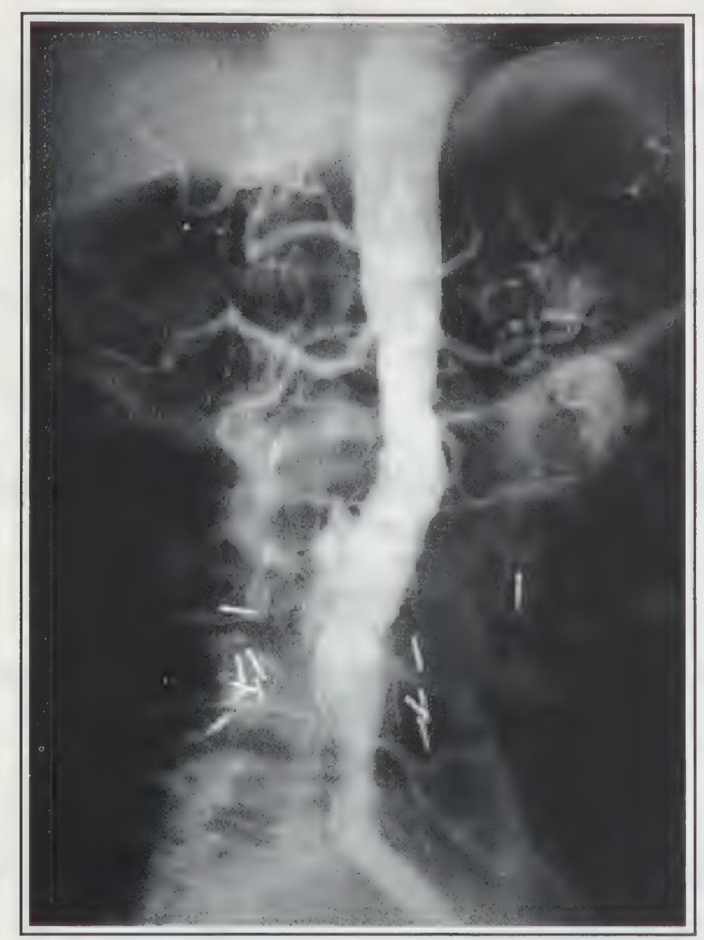


Figure 2: Antero-posterior view aortogram. A contrast leak is observed on the right side of the aorta, originated in the proximal aorto-graft anastomosis.



Figure 3: Lateral view aortogram.

TABLE: 1 ETIOLOGY OF URETEROARTERIAL FISTULA
•Urologic:
•Chronic indwelling ureteral stent
•Hydroureteronephrosis
•Chronic infection
•Ureterolithiasis
•Vascular:
•Significant aortoiliac disease
•Vascular surgery with prosthetic graft
•chronic infection
•Pelvic Malignancy
•Pelvic Radiotheraphy

At surgery, findings were of a huge aortic pseudoaneurysm of the proximal anastomosis that infiltrated distally to the inflammatory process of the right ureter. After dissection, the uretero-aortic stump fistula was fully appreciated. After proximal and distal vascular control, the aortobifemoral graft was removed and the descending aorta was ligated distal to the inferior mesenteric artery and at the left iliac artery. The urologist performed a right nephrostomy and a cystostomy. Once the abdominal wall was closed an axillaro-femoral graft bypass with gore-tex was performed subcutaneously. The patient was discharged from the hospital ten days later, to be followed at the outpatient department.

DISCUSSION:

UAF is a rare condition that usually develops as the result of several diseases, such as retroperitoneal fibrosis post radiotherapy, cancer, indwelling ureteral stents, ureteral obstruction or nephrolithiasis and infection. Besides the vascular fistulas, ureter related fistula can occur with the sigmoid colon and vagina.[1,8] (Table I)

The first three reported cases were in 1939 when ureteral catheters were used for extended periods in the treatment of obstructive pyelonephritis during pregnancy. The infection process and the external pressure of the gravid uterus over the ureter placed these otherwise healthy patients at high risk for fistula formation. Vascular repair of the aorta and iliac vessels have been well documented in the literature as causes for the formation of UAF. When the aortic graft is placed anteriorly to the ureter, pulsatile forces may lead to pressure necrosis and erosion of the ureter. Only one case has been reported in the literature of a patient with UAF who had no history of surgery, endoscopy or any other procedure[9].

Diagnosis of the UAF is rarely made before operation. In our case the fistula occurred after a complication of vascular surgery with damage and repair of the right ureter. The creation of the UAF was very

much aided by the presence of infection after the removal of the right limb of the aorto-bifemoral gore-tex by pass. Routine studies cannot be relied on to confirm the diagnosis unless a high index of suspicion exists. Massive bleeding is almost always the most common finding manifesting itself as gross hematuria. Different radiographic studies are useful for the diagnosis[10]. Once the fistula is diagnosed, the logical approach to the management of the UAF should include early surgical intervention, division of the fistula and repair of the urinary and vascular system. The surgeon must be prepared to proceed with different surgical procedures such as simple ligation, patch grafting and or removal of previous graft in the artery affected with revascularization of the extremity. For the repair of the ureter, it will depend at which level it has been damaged. Some cases have been described in the literature where renal autotransplantation is the best measure for ureteral repair when it is widely damaged at its midportion[11]. If infection is present, a temporal nephrostomy is an acceptable choice. A damaged ureter at it's distal portion without evidence of infection can be repaired with a end to end ureteral anastomosis.

The prognosis of these cases has improved in recent years due to advances in critical care management and improved vascular techniques. Nonetheless, an UAF remains a technically challenging problem.

Resumen: *La fistula aortoureteral es una condición de rara frecuencia. Por la gravedad de esta condición siempre se debe tener presente como diagnóstico diferencial en pacientes con historial previo de cirugia vascular aortofemoral y presencia súbita de hematuria. En este artículo presentamos el caso de un paciente con hematuria severa secundaria a una fístula del injerto aortobifemoral con el ureter derecho. La infección de la pata derecha del injerto y su localización adyacente al ureter se postula como la causa de la creación y final desarrollo de la fístula. En este artículo se presenta detalladamente la evolución del paciente, los estudios diagnósticos asi como el tratamiento final recibido.*

REFERENCES

1. Bullock A, Andriole G; Neuma N, et al. Renal autotransplantation in the management of a ureteroarterial fistula: a case repor and review of the literature. Journal Vascular Surgery 15: 436-41, 1992.
2. Kar et al. Ureteral common iliac artery fistula: a complication of internal double-J ureteral stent. Journal Urology 132: 113,1984.
3. Lytton et al. Ureteral obstruction following aorto-femoral bypass. 59: 918-22,1966.
4. Petrone et al. Ureteral obstruction secondary to aortic femoral bypass. Ann Surgery 179: 192-6, 1974.
5. Taylor et al. Mycotic aneurysm in common iliac artery with rupture into right ureter. Journal Urology. 42: 21, 1939.
6. Kar et al. Ureteroarterial and ureterosigmoid fistula associated with polyethylene indwelling ureteral stents. Journal Urology. 132: 177, 1984.
7. Whitmore et al. Uretero-arterial and Uretero-vaginal fistula: a case report. Urology 21: 184, 1954.
8. Hamer et al. Fatal ureteral hemorrhage due to erosion into iliac artery. Report of a case ocurring indwelling catheter drainage for pyelitis of pregnancy. Trans. Amer. Ass. Genitourin. Surg. 32: 177,1939.
9. Rennick et al. Spontaneous rupture of an iliac artery aneurysm into a ureter: a case report and review of the literature. Journal Urology. 116: 111, 1976.
10. Jafri et al. Urographic and computed tomographic demostration of ureteroarterial fistula. Urology Radiology. 9: 47-9, 1987.
11. Sicard et al. Renal autotransplantation: alternative to standard renal revascularization procedures. Surgery 104: 624-30,1988.

After 55 years, we’re discove

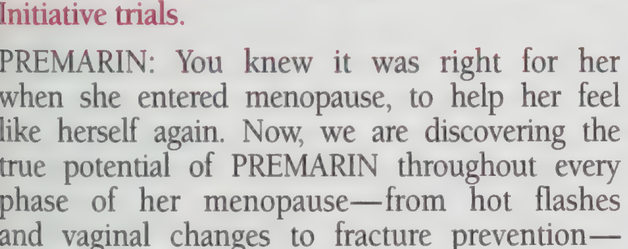
That’



ng more.

why Nothing Else Is Premarin.™

PREMARIN is grounded in 5 decades of experience, and has been used by tens of millions of women. Initially, PREMARIN was prescribed to dramatically reduce the troublesome symptoms of menopause, helping women feel better and enjoy life. Through the years, researchers began to ask questions about the role of PREMARIN in many diseases affecting menopausal women. These questions initially led us to recognize the role of PREMARIN in the prevention and management of osteoporosis, including the reduction of fracture risk.[1]



Now, the PREMARIN family of products is the hormone replacement therapy being used in several large-scale studies on the consequences of menopause, including the well-publicized Women's Health Initiative trials.

PREMARIN: You knew it was right for her when she entered menopause, to help her feel like herself again. Now, we are discovering the true potential of PREMARIN throughout every phase of her menopause—from hot flashes and vaginal changes to fracture prevention—and beyond.

PREMARIN is indicated for the prevention and management of osteoporosis and the treatment of moderate to severe vasomotor symptoms associated with menopause.

Contraindications: Estrogens should not be used in women (or men) with any of the following conditions: 1) known or suspected pregnancy, 2) known or suspected breast cancer, 3) known or suspected estrogen-dependent neoplasia, 4) undiagnosed abnormal genital bleeding, 5) active thrombophlebitis or thromboembolic disorders.

PREMARIN should not be used in patients hypersensitive to its ingredients.

Note: Estrogens have been reported to increase the risk of endometrial carcinoma in postmenopausal women. This finding refers to estrogens given without progestin.

Please see adjacent page for brief summary of Prescribing Information.

For my patients, it's

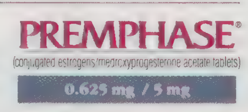
PREMARIN® (conjugated estrogens tablets, USP) *Family of Products*



PREMARIN® 0.625 mg/g (conjugated estrogens) VAGINAL CREAM in a nonliquefying base







PREMPRO™ 5 mg NOW AVAILABLE!

PREMPRO™ (conjugated estrogens/medroxyprogesterone acetate tablets) Brief Summary

(For Full Prescribing Information and Patient Information, See Package Circulars.)

Description: PREMPRO™ (conjugated estrogens/medroxyprogesterone acetate tablets) therapy consists of a single tablet containing 0.625 mg of the conjugated estrogens found in Premarin®, and 2.5 mg of medroxyprogesterone acetate (MPA), for oral administration.

ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA IN POSTMENOPAUSAL WOMEN. THIS FINDING REFERS TO ESTROGENS GIVEN WITHOUT PROGESTIN.

Progestins taken with estrogen drugs significantly reduce but do not eliminate this risk. Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

ESTROGENS/PROGESTINS SHOULD NOT BE USED DURING PREGNANCY.

There is no indication for estrogen therapy during pregnancy or during the immediate postpartum period. Estrogen therapy during pregnancy is associated with an increased risk of congenital defects in the reproductive organs of the fetus, and possibly other birth defects. Estrogens are not indicated for the prevention of postpartum breast engorgement.

Studies of women who received diethylstilbestrol (DES) during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life. The 1985 DES Task Force concluded that use of DES during pregnancy is associated with subsequent increased risk of breast cancer in the mothers, although a causal relationship remains unproven and the observed level of excess risk is similar to that for a number of other breast cancer risk factors.

Several reports also suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias, 5 to 8 per 1000 male births in the general population, may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risk to exposed female fetuses; some of these drugs induce mild virilization of the external genitalia of the female fetus. If the patient is exposed to PREMPRO™ (conjugated estrogens/medroxyprogesterone acetate) during pregnancy, or if she becomes pregnant while taking these drugs, she should be apprised of the potential risks to the fetus.

Estrogens are ineffective for the prevention or treatment of threatened or habitual abortion. There is no adequate evidence that progestational agents are effective in preventing habitual abortion when such drugs are given during the first trimester of pregnancy. Furthermore, in the vast majority of women, the cause of abortion is a defective ovum, which progestational agents could not be expected to influence. In addition, the use of progestational agents with their uterine-relaxant properties, in patients with fertilized defective ova, may cause a delay in spontaneous abortion.

Indications and Usage: Indicated in women with an intact uterus for the treatment of moderate to severe vasomotor symptoms associated with the menopause; treatment of vulvar and vaginal atrophy; prevention of osteoporosis (since estrogen administration is associated with risks as well as benefits, patient selection ideally should be based on prospective identification of risk factors for developing osteoporosis).

Contraindications: 1) Known or suspected pregnancy, including use for missed abortion or as a diagnostic test for pregnancy (see Boxed Warning). Estrogen or progestin may cause fetal harm when administered to a pregnant woman. 2) Known or suspected cancer of the breast. 3) Known or suspected estrogen-dependent neoplasia. 4) Undiagnosed abnormal genital bleeding. 5) Active or past history of thrombophlebitis, thromboembolic disorders, or stroke. 6) Liver dysfunction or disease.

PREMPRO should not be used in patients hypersensitive to its ingredients.

Warnings: ALL WARNINGS BELOW PERTAIN TO THE USE OF THIS COMBINATION PRODUCT. (Based on experience with estrogens and/or progestins):

Induction of malignant neoplasms

Breast cancer. Some studies have reported a moderately increased risk of breast cancer (relative risk of 1.3 to 2.0) in those women on estrogen replacement therapy (ERT) taking higher doses, or in those taking lower doses for prolonged periods of time, especially >10 years. The majority of studies, however, have not shown an association in women who have ever used ERT. The effect of added progestins on the risk of breast cancer is unknown, although a moderately increased risk in those taking combination estrogen/progestin therapy has been reported. Other studies have not shown this relationship.

Endometrial cancer. The reported endometrial cancer risk among users of unopposed estrogen was about 2- to 12-fold or greater than in nonusers and appears dependent on treatment duration and estrogen dose. There is no significant increased risk associated with estrogen use for <1 year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for 5 years or more. In one study, persistence of risk was demonstrated for 10 years after cessation of estrogen treatment. In another study, a significant decrease in the incidence of endometrial cancer occurred 6 months after estrogen withdrawal.

A large clinical trial demonstrated that MPA administered with Premarin markedly reduces the incidence of endometrial hyperplasia, a possible precursor of endometrial cancer. Endometrial hyperplasia has been reported in a large clinical trial to occur at a rate of approximately 1% or less with PREMPRO. Studies have also demonstrated a reduced risk of endometrial cancer when a progestin is given with ERT.

Clinical surveillance of all women taking estrogen/progestin combinations is important. Adequate diagnostic measures should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

Thromboembolic disorders and other vascular problems. In some epidemiological studies, women on estrogen replacement therapy, given alone or in combination with a progestin, have been reported to have an increased risk of thrombophlebitis, and/or thromboembolic disease, although the evidence is conflicting. The physician should be aware of the possibility of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism, and pulmonary embolism) during hormone replacement therapy and be alert to their earliest manifestations. Should any of these occur or be suspected, hormone replacement therapy should be discontinued immediately. Women who have risk factors for thrombotic disorders should be kept under careful observation.

Effects during pregnancy. Use in pregnancy is not recommended. See Boxed Warning.

Gallbladder disease. Two studies have reported a 2- to 4-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.

Elevated blood pressure. Occasional blood pressure increases during ERT have been attributed to idiosyncratic reactions to estrogens. More often, blood pressure has remained the same or has dropped. Postmenopausal estrogen use does not increase the risk of stroke. Nonetheless, blood pressure should be monitored at regular intervals with estrogen use.

Hypercalcemia. Estrogen therapy may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

Visual abnormalities. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. Withdraw medication if papilledema or retinal vascular lesions occur.

Precautions: GENERAL

Based on experience with estrogens and/or progestins:

Cardiovascular Risk. A causal relationship between ERT and reduction of cardiovascular disease in postmenopausal women has not been proven. The effect of added progestins on this putative benefit is not yet known.

Many published studies suggest that there may be a cause-effect relationship between postmenopausal oral ERT *without added progestins* and a decrease in cardiovascular disease. Although most of the observational studies which assessed this statistical association have reported a 20% to 50% reduction in coronary heart disease risk and associated mortality in estrogen takers, the following should be considered when interpreting these reports: Because only one of these studies was randomized and it was too small to yield statistically significant results, all relevant studies were subject to selection bias. Thus, the apparently reduced risk of coronary artery disease cannot be attributed with certainty to ERT. It may instead have been caused by life-style and medical characteristics of the women studied with the result that healthier women were selected for estrogen therapy. Ongoing and future large-scale randomized trials may fail to confirm this apparent benefit.

Current medical practice often includes the use of concomitant progestin therapy in women with intact uteri. While the effects of added progestins on the risk of ischemic heart disease are not known, MPA at the dose in PREMPRO™ (conjugated estrogens/medroxyprogesterone acetate tablets) attenuates much of the favorable effect of conjugated estrogens on HDL levels, although it maintains the favorable effect of conjugated estrogens on LDL levels (see **Clinical Pharmacology** in Full Prescribing Information).

The effects of added progestins on the risk of breast cancer are also unknown, however, available epidemiologic evidence suggests that progestins may enhance the moderately increased breast cancer risk reported with prolonged ERT (see **Warnings** section).

The safety data regarding PREMPRO were obtained primarily from clinical trials and epidemiologic studies of postmenopausal Caucasian women, who were at generally low risk for cardiovascular disease and higher than average risk for osteoporosis. The safety profile of PREMPRO derived from these study populations cannot necessarily be extrapolated to other populations of diverse racial and/or demographic composition. When considering prescribing PREMPRO, physicians are advised to weigh the potential benefits and risks of therapy as applicable to each individual patient.

Use in hysterectomized women. Data do not support the use of combined estrogen/progestin in postmenopausal women without a uterus; possible risks may be associated with this combined regimen. Potential risks include some deterioration in glucose tolerance and less favorable effects on lipid metabolism as compared to lipid effects of Premarin® (conjugated estrogens tablets, USP) alone.

Physical examination. A complete medical and family history should be taken prior to the initiation of therapy with special reference to blood pressure, breast, abdomen, and pelvic organs, as well as a Papanicolaou smear. Generally, estrogen should not be prescribed for longer than one year without another physical examination being performed.

Fluid retention. Conditions influenced by fluid retention, such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.

Uterine bleeding. Certain patients may develop abnormal uterine bleeding; if undiagnosed, adequate diagnostic measures are indicated. (See **Warnings.**)

Advise pathologist of estrogen/progestin therapy when relevant specimens are submitted.

Based on experience with estrogens:

Familial hyperlipoproteinemia. Estrogen therapy may be associated with massive elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects of lipoprotein metabolism.

Hypercoagulability. Women taking ERT may have hypercoagulability primarily related to decreased antithrombin activity. This appears dose- and duration-dependent and is less pronounced than that associated with oral contraceptive use. Also, postmenopausal women tend to have changes in levels of coagulation parameters at baseline compared to premenopausal women. There is insufficient information on hypercoagulability in women who have had previous thromboembolic disease.

Mastodynia. Certain patients may develop this undesirable manifestation of estrogenic stimulation.

Based on experience with progestins:

Lipoprotein metabolism. See **Clinical Pharmacology** in Full Prescribing Information.

Impaired glucose tolerance. See *Use in hysterectomized women,* above.

Depression. Observe patients who have a history of depression and discontinue the drugs if depression recurs to a serious degree.

DRUG/LABORATORY TEST INTERACTIONS—1) Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity. 2) Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. 3) Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin). 4) Increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglyceride levels. 5) Impaired glucose tolerance. Observe diabetic patients carefully. 6) Reduced response to metyrapone test. 7) Reduced serum folate concentration. 8) Aminoglutethimide administered concomitantly with MPA may significantly depress the bioavailability of MPA.

CARCINOGENESIS, MUTAGENESIS AND IMPAIRMENT OF FERTILITY. Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breasts, uterus, cervix, vagina, testis, and liver. (See **Contraindications** and **Warnings.**)

Female rats exposed to dietary dosages of up to 5000 μg/kg/day of MPA (50 times higher—based on AUC values—than the level observed experimentally in women taking 10 mg of MPA), exhibited a dose-related increase in pancreatic islet cell tumors (adenomas and carcinomas). Pancreatic tumor incidence was increased at 1000 and 5000 μg/kg/day, but not at 200 μg/kg/day.

A decreased incidence of spontaneous mammary gland tumors was observed in all three MPA-treated groups, compared to controls, in the two-year rat study. This decreased incidence may be linked to the significant decrease in serum prolactin concentration observed in rats.

Beagle dogs treated with MPA developed mammary nodules, some of which were malignant. Although nodules occasionally appeared in control animals, they were intermittent in nature, whereas the nodules in the drug-treated animals were larger, more numerous, persistent, and there were some breast malignancies with metastases. Progestogens stimulate synthesis and release of growth hormone (GH) in dogs, resulting in stimulation of mammary growth and tumors. In contrast, GH in humans is not increased, nor does GH have any significant mammotrophic role. Therefore, the MPA-induced increase of mammary tumors in dogs probably has no significance to humans. No pancreatic tumors occurred in dogs.

PREGNANCY CATEGORY X—Estrogens/progestins should not be used during pregnancy. See **Contraindications** and Boxed Warning.

NURSING MOTHERS—Generally, drugs should not be given to nursing mothers unless clearly necessary since many drugs are excreted in human milk. Estrogen administration to nursing mothers may decrease the milk's quantity and quality. Detectable amounts of progestin have been identified in the milk of mothers receiving the drug. The effect of this on the nursing infant is not known.

Adverse Reactions: (See **Warnings** regarding induction of neoplasia, adverse effects on the fetus, increased incidence of gallbladder disease, elevated blood pressure, thromboembolic disorders, cardiovascular disease, visual abnormalities, and hypercalcemia and **Precautions** for cardiovascular disease.)

The following adverse reactions have been reported with estrogen and/or progestin therapy: *Genitourinary system.* Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow, breakthrough bleeding, spotting, change in amount of cervical secretion, premenstrual-like syndrome, cystitis-like syndrome, increase in size of uterine leiomyomata, vaginal candidiasis, amenorrhea, changes in cervical erosion. *Breasts.* Tenderness, enlargement, galactorrhea. *Gastrointestinal.* Nausea, cholestatic jaundice, changes in appetite, vomiting, abdominal cramps, bloating, increased incidence of gallbladder disease, pancreatitis. *Skin.* Chloasma or melasma that may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism, itching, urticaria, pruritus, generalized rash, rash (allergic) with and without pruritus, acne. *Cardiovascular.* In susceptible individuals, change in blood pressure, thrombophlebitis, pulmonary embolism, cerebral thrombosis and embolism. *CNS.* Headache, dizziness, mental depression, nervousness, migraine, chorea, insomnia, somnolence. *Eyes.* Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis. Steepening of corneal curvature, intolerance of contact lenses. *Miscellaneous.* Increase or decrease in weight, edema, changes in libido, fatigue, backache, reduced carbohydrate tolerance, aggravation of porphyria, pyrexia, anaphylactoid reactions, anaphylaxis.

Acute Overdosage: May cause nausea and vomiting; withdrawal bleeding may occur in females.

Dosage and Administration: PREMPRO 0.625 mg/2.5 mg therapy consists of a single tablet to be taken once daily.

For moderate to severe vasomotor symptoms, vulvar and vaginal atrophy—reevaluate patients at 3-month to 6-month intervals to determine if treatment is still necessary.

For prevention of osteoporosis—monitor patients closely for signs of endometrial cancer; appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

This brief summary is based on PREMPRO CI4664-3, Revised 5/21/97.

Reference: 1. Data on file, Wyeth-Ayerst Laboratories. PREMARIN® (conjugated estrogens tablets, USP) Prescribing Information.

Reporte de Casos:

Recognition of Hemophilia A in an Elderly Patient

William Cáceres, MD, FACP; Shirley McCurdy, MT

Summary: *Hemophilia A (classic hemophilia) is an hereditary coagulation disorder characterized by the absence, severe deficiency, or defective functioning of plasma coagulation factor VIII. It is inherited in an X-linked recessive manner and occurs almost exclusively in males. The first manifestations of bleeding are usually first noted as a young child since most of the patients with hemophilia A have a profound deficiency of factor VIII (less than 1% of normal value). However, in mild hemophilia (5-25% of normal level of factor VIII) the condition may escape detection with many of the patients developing bleeding only after trauma or surgery. Hemophilia A is the result of a recent genetic mutation in approximately one third of patients, for whom often there is no family history of a bleeding disorder. Here we present an elderly male patient with spontaneous bleeding in an extremity that has coagulation studies consistent with the diagnosis of hemophilia A. Physicians must be aware that mild hemophilia can present in this unusual manner and should consider this possibility in patients that have unexplained bleeding even if there is no clear personal or family history of an hereditary coagulation disorder.*

INTRODUCTION

Hemophilia A (classic hemophilia) is an hereditary coagulation disorder and has no ethnic or geographic limitations, with an incidence of 20 per 100,000 male births (1). It is inherited in an X-linked recessive manner and occurs almost exclusively in males, in whom the effects of one defective copy of the gene cannot be overcome by the presence of a second allele. This condition is characterized by the absence, severe deficiency, or defective functioning of plasma coagulation factor VIII (antihemophilic factor) (2). It must be differentiated from hemophilia B (Christmas disease), which is clinically indistinguishable from hemophilia A, but instead is characterized by a deficiency in factor IX (3). Hemophilia A is the result of a recent genetic mutation in approximately one third of patients, for whom there is often no family history of a bleeding disorder (4).

Among patients with hemophilia A treated in the United States, 60% of cases have a severe deficiency of factor VIII (less than 1% of normal level) (5). The other patients have a moderate level of factor VIII (1 to 4 % of the normal level) or mild hemophilia (5 to 25 % of normal level). The number of subjects with mild disease is not known, since many of them have no considerable bleeding and escape detection. Mild hemophilia may only be recognized in adults after trauma or surgery, and there may be no history of bleeding (6).

Patients with hemophilia A usually present the first manifestations of bleeding in the form of hemarthroses, muscle bleeding and easy bruising as a young child, since most of them have a profound deficiency of factor VIII. We diagnosed hemophilia A in a 63 year old male veteran with no family history of a bleeding disorder. This case report emphasizes the importance to consider this condition even in elderly patients who present with unexplained bleeding.

CASE REPORT

A 63 year old male patient with essential hypertension using Enalapril 5 mg po qd and congestive heart failure using Digoxin 0.2 mg po qd and Furosemide 20 mg po bid presented to our Institution with a large spontaneous hematoma in the right thigh with inability to walk due to marked edema. The patient denied trauma or recent surgery, and was not using aspirin, alcohol, or anticoagulant drugs. He had no personal or family history of bleeding disorders; one brother died of laryngeal cancer and a daughter suffered rheumatoid arthritis. His other son had good health. The only remarkable bleeding history was when he entered the Army and had a tooth extracted, which required sutures and packing one day after the extraction due to uncontrolled bleeding. The patient never had received blood transfusions. He served in the Korean War while in the Army.

In physical exam, the patient presented a huge soft tissue mass with associated purpura in the medical aspect of the entire right thigh that extended to the knee. There were no other hematomas, hemarthrosis or petechiae and the other positive finding was a grade II/VI holosystolic murmur.

Department of Hematology-Oncology, Veterans Administration Medical Center, One Veterans Plaza, San Juan, Puerto Rico 00927-5800 (787) 758-9217 - TEL. (787)758-7348 (FAX)

The white blood cell count was 9300/ ul, the hemoglobin 9.5 g/ dl, the hematocrit 28.2 %, and the platelet count 223,000. His hemoglobin six months before was 13.8 g/ dl. Coagulation studies are depicted in Table I. It is noteworthy that the patient presented a prolonged APTT that corrected with a 1:1 mixture with normal plasma, with a marked decrease in factor VIII levels and an increased von Willebrand factor level. Incubation for 2 hours at 37 C of a mixture of the patient's plasma with normal plasma did not result in further prolongation of the APTT or in a further decrease in factor VIII activity, which is evidence against the presence of factor VIII inhibitors in this patient. In view of the mild prolongation of the bleeding time, platelet aggregation studies were performed and were normal: ristocetin aggregation 90.0 (NV 76.3-99.9), ADP 68.8 (NV 68-91.6) , collagen 87.5 (NV 63.8-91), epinephrine 78.8 (NV 67- 97).

Table I.
Coagulation Studies

	PLT	PT (s)	APTT (s)	APTT 1:1	BT (min)	FVIII activity	FV activity	VWF: RCo	VWF: Ag
Patient	223	11.7	67.8	34.8	10.5	6 %	168 %	>200 %	156 %
Normal	>150	10.6-12.6	23.1-35.5	-	3-9	50-100	50-150	46-168	50-160

PLT:platelet count; PT:prothrombin time; APTT: activated partial thromboplastin time; BT:bleeding time; FVIII:factor VIII; FV:factor V; VWF:Rco:ristocetin cofactor activity; VWF:Ag:von Willebrand factor antigen

The patient was treated with fresh frozen plasma 15 cc/ kg on arrival, and after factor VIII levels were available, he received cryoprecipitate with resolution of bleeding and a marked improvement in the leg edema. The patient had been stable with follow up in Hematology Clinics with plans to receive factor VIII concentrate infusion if has rebleeding.

DISCUSSION

We have presented an elderly patient with spontaneous bleeding and development of a large hematoma in a muscle showing coagulation studies consistent with the diagnosis of classic hemophilia. Although this late presentation can be explained on basis of a mild deficiency of factor VIII, it is interesting that the patient had no personal or family history of a bleeding diathesis. As stated before, in mild hemophilia in adults there may be no prior bleeding. The disease can be the result of a recent genetic mutation: there can be cases with no family history (4,6).

The diagnosis of hemophilia A should be suspected whenever unusual bleeding is encountered in a male patient that has a normal platelet count and a normal prothrombin (PT) time, but a prolonged activated partial thromboplastin time (APTT). There is correction of the APTT on a 1:1 mixture of the patient's plasma with normal plasma. The bleeding time usually is normal in classic hemophilia but a few patients may show a mild or moderately prolonged bleeding time (7). A factor VIII assay must be performed for a definitive diagnosis, since many other medical conditions can cause bleeding and a prolonged partial thromboplastin time. Hemophilia A must be differentiated from von Willebrand's disease, hemophilia B, factor VIII inhibitors (which is a more common initial presentation in adults), factor XI deficiency and other conditions by specific coagulation tests and assays.

Patients with von Willebrand's disease also have a factor VIII deficiency but as a consequence of decreased survival of the factor in plasma (8). Factor VIII circulates in plasma in a noncovalent complex with von Willebrand factor. The distinction of hemophilia A and von Willebrand's disease can be made usually by measuring either the von Willebrand factor antigen or the ristocetin cofactor activity, which is the ability of the von Willebrand factor to support platelet aggregation in the presence of ristocetin (9). Von Willebrand factor antigen and ristocetin cofactor activity are reduced in most patients with von Willebrand's disease and normal or increased in patients with hemophilia A. This patient had a high ristocetin cofactor activity and normal-high VWF: Antigen with a low factor VIII activity and normal aggregation of platelets with ristocetin, which supports the diagnosis of hemophilia A. He presented a prolongation of the bleeding time, which is a hallmark for von Willebrand's disease, but a few patients with hemophilia A can have a mild prolongation of the bleeding time (7). Acquired hemophilia due to factor VIII inhibitors is a most common presentation in adults, but in this patient our screening as well as confirmatory tests did not detect the presence of an inhibitor.

The use of the above distinctions can lead to an incorrect diagnosis in rare patients with a variant form of von Willebrand's disease in which the von Willebrand factor does not bind factor VIII (9, 10). The patients with this autosomally transmitted variant have a persistent increase in factor VIII after infusion of factor VIII concentrate, in contrast to patients with classic hemophilia that have a half life of 10 hours or less of the infused factor VIII. This variant mimics hemophilia A on standard laboratory tests, and measurements of factor VIII-von Willebrand factor binding are needed to establish the diagnosis. However, due to the presence of deep and superficial muscle bleeding in this patient and the low level of factor VIII with high levels of von Willebrand's factor, the most probable diagnosis in this patient is Hemophilia A.

In conclusion, this case report of an elderly patient with findings consistent with classic hemophilia should make physicians aware of this possibility even in patients with no clear personal or family history of an hereditary coagulation disorder.

Resumen: *Hemofilia A (hemofilia clásica) es un desorden hereditario de coagulación que se carateriza por la ausencia, deficiencia severa, o función defectuosa del factor VIII plasmático. Esta condición se hereda de una forma recesiva ligada al cromosoma X y ocurre casi exclusivamente en varones. Las primeras manifestaciones de sangrado en la forma de hemartrosis, sangrado en músculos y hematomas ocurren usualmente a una edad temprana en el niño ya que la mayoría de los pacientes con hemofilia A tienen una deficiencia profunda del factor VIII (menos de 1 % del valor normal). Sin embargo, en hemofilia leve (5 a 25 % del nivel normal de factor VIII), la condición puede escapar detección con muchos de los pacientes desarrollando sangrado solamente luego de trauma o cirugía. Hemofilia A es el resultado de una mutación genética reciente en aproximadamente un tercio de los pacientes, por lo cual frecuentemente no hay historial familiar de un desoden de sangrado. Presentamos en este artículo un paciente envejeciente masculino con sangrado espontáneo en una extremidad con estudios de coagulación consistentes con el diagnóstico de hemofilia A. Los médicos debemos estar conscientes que hemofilia leve se puede presentar de una forma poco usual y deben considerar esta condición en pacientes que tienen sangrado sin explicación aún sin haber un historial personal o familiar de un desorden hereditario de coagulación.*

REFERENCES

1. Levine PH. Clinical manifestations and therapy of hemophilias A and B. In: Colman RW,Hirsch J, Marder VJ, Salzman EW, eds. Hemostasis and Thrombosis: Basic Principles and Clinical Practice, 2nd ed., Philadelphia, JB Lippincott,1988; 97-111.

2. White GC, Shoemaker CB: Factor VIII gene and hemophilia A. Blood 1989;73:1-12.

3. Bloom AL. Inherited disorders of blood coagulation. In: Bloom AL, Thomas DP, eds. Haemostasis and Thrombosis, 2nd ed., Edinburg,Scotland, Churchill Livingstone, 1987; 393-436.

4. Hoyer LW: Hemophilia A. N Engl J Med 1994; 330:38-47.

5. Levine PH, Brettler DB. Clinical aspects and therapy for Hemophilia A. In: Hoffman R, Benz EJ, Shattil SJ, Furie B, Cohen HJ, eds. Hematology: Basic Principles and Practice, New York, Churchill Livingstone , 1992:1290.

6. Kitchens CS. Occult hemophilia. John Hopkins Med J 1980; 146:255-9.

7. Roberts HR, Jones MR. Hemophilia and related conditions. In: Williams WJ, Beutler E, Erslev AJ, Lichtman MA, eds. Hematology, 4th ed.,New York, McGraw Hill, 1990:1458.

8. Weiss HJ, Sussman I, Hoyer LW: Stabilization of factor VIII in plasma by the von Willebrand factor. J Clin Invest 1977; 60:390.

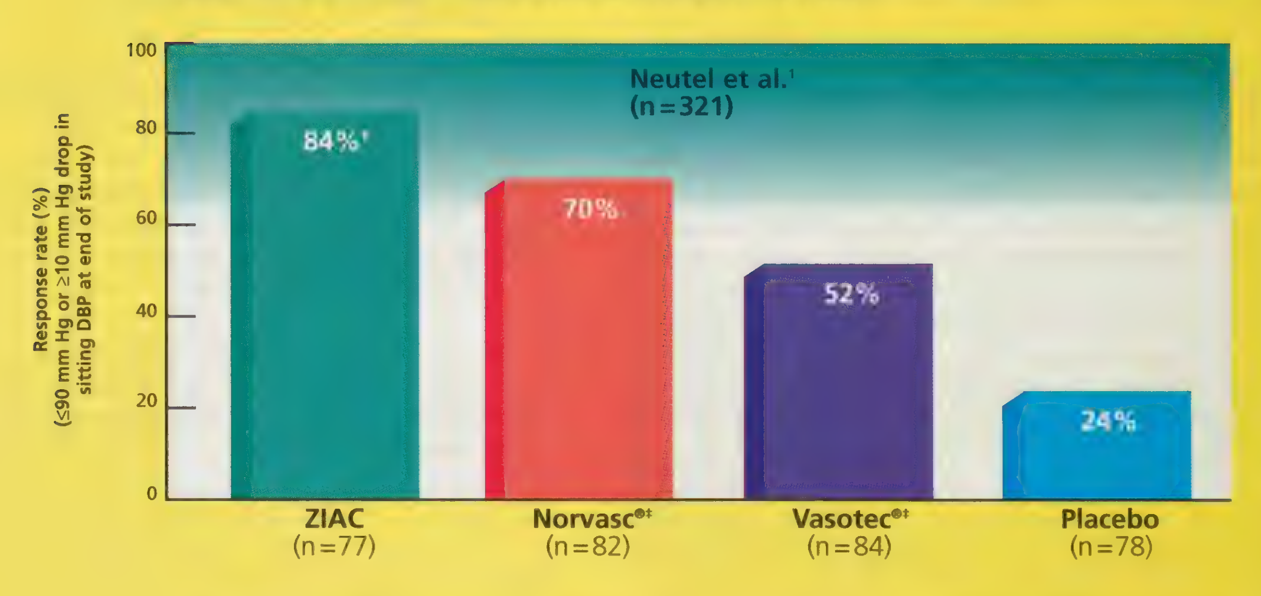
9. Nishino M, Girma JP, Rothschild C, Fressinaud E, Meyer D: New variant of von Willebrand disease with defective binding to factor VIII. Blood 1989; 74:1591-1599.

10. Mazurier C, Dieval J, Jorieux S, Delobel J, Goudeman M : A new von Willebrand factor defect in a patient with factor VIII deficiency. Blood 1990; 75:20-26.

Hypertension control that lets patients stay...

ZIACTIVE™

ZIAC demonstrated a response rate up to 84% in controlled trials[1,2]*



Neutel et al[1]: 18-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group dose-escalation study of patients with mild to moderate hypertension. Drugs were titrated upward to achieve a sitting DBP ≤90 mm Hg. Dose ranges were: ZIAC—2.5 to 10 mg qd; Vasotec—5 and 10 mg qd, and 10 and 20 mg bid; or Norvasc—2.5 to 10 mg qd.

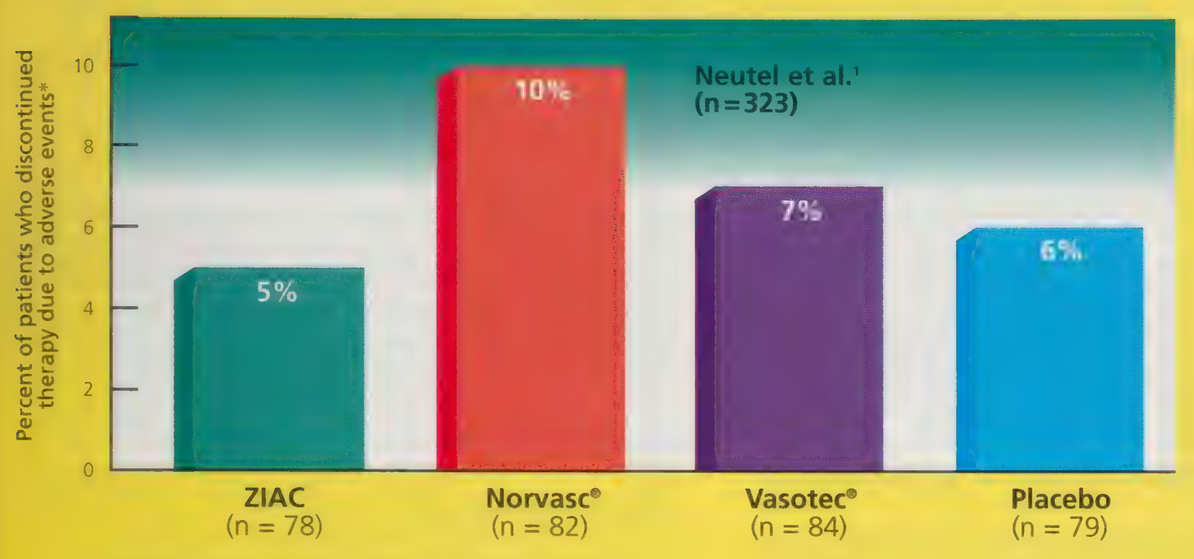
In a second randomized controlled trial involving 218 patients, the overall response rates were: ZIAC 71% ($P<0.01$ *vs* Vasotec), Vasotec 45%, Norvasc 69%.[2]

*Response rates in pivotal trials were 2.5 mg—61%, 5 mg—73%, and 10 mg—80%.[3]

† $P<0.05$ *vs* Norvasc; $P<0.0001$ *vs* Vasotec; $P<0.0001$ *vs* placebo.

‡Norvasc (amlodipine besylate) is a registered trademark of Pfizer Inc; Vasotec (enalapril maleate) is a registered trademark of Merck & Co., Inc.

ZIAC: Consistently low discontinuation rates due to adverse events[1,2]



*Differences not statistically significant.

ZIAC: The benefits of low-dose design[1-4]

- Minimizes dose-related beta-blocker-associated and diuretic-associated side effects
- Placebo-like side-effect profile, including low incidence of cough (1.5%), peripheral edema (0.9%), and headache (0.4%)
- No significant change in mean levels of total cholesterol, serum glucose, or serum potassium
- Clinically insignificant changes in mean serum triglycerides and serum uric acid

In pivotal clinical studies, the most common side effects with ZIAC were dizziness (3.2%) and fatigue (3.0%). ZIAC is contraindicated in patients in cardiogenic shock, overt cardiac failure, second- or third-degree AV block, marked sinus bradycardia, anuria, and hypersensitivity to either component of this product or to other sulfonamide-derived drugs. Patients with bronchospastic pulmonary disease should, in general, not receive beta-blockers.





Hardworking therapy patients hardly notice

Please see brief summary of Prescribing Information on adjacent page.

First-line therapy option

ZIAC

(bisoprolol fumarate-hydrochlorothiazide)
2.5, 5, & 10 mg Tablets with 6.25 mg HCTZ

Hardworking therapy patients hardly notice

References: 1. Neutel JM, Rolf CN, Valentine SN, et al. Low-dose combination therapy as first line treatment of mild-to-moderate hypertension: the efficacy and safety of bisoprolol/HCTZ versus amlodipine, enalapril, and placebo. *Cardiovasc Rev Rep.* 1996;17:33-45. **2.** Prisant LM, Weir MR, Papademetriou V, et al. Low-dose drug combination therapy: an alternative first-line approach to hypertension treatment. *Am Heart J.* 1995;130:359-366. **3.** DeQuattro V, Weir MR. Bisoprolol fumarate/hydrochlorothiazide 6.25 mg: a new low-dose option for first-line antihypertensive therapy. *Adv Ther.* 1993; 10:197-206. **4.** Zachariah PK, Messerli FH, Mroczek W. Low-dose bisoprolol/hydrochlorothiazide: an option in first-line antihypertensive treatment. *Clin Ther.* 1993;15:779-787.

Brief Summary

ZIAC® (Bisoprolol Fumarate and Hydrochlorothiazide) Tablets

FOR FULL PRESCRIBING INFORMATION, PLEASE CONSULT PACKAGE INSERT.

DESCRIPTION

ZIAC (bisoprolol fumarate and hydrochlorothiazide) is indicated for the treatment of hypertension. It combines two antihypertensive agents in a once-daily dosage: a synthetic $beta_1$-selective (cardioselective) adrenoceptor blocking agent (bisoprolol fumarate) and a benzothiadiazine diuretic (hydrochlorothiazide).

CLINICAL PHARMACOLOGY

At doses ≥ 20 mg bisoprolol fumarate inhibits $beta_2$-adrenoreceptors located in bronchial and vascular musculature. To retain relative selectivity, it is important to use the lowest effective dose.

CONTRAINDICATIONS

Cardiogenic shock, overt cardiac failure (see **WARNINGS**), second- or third-degree AV block, marked sinus bradycardia, anuria, and hypersensitivity to either component of this product or to other sulfonamide-derived drugs.

WARNINGS

Cardiac Failure: Beta-blocking agents should be avoided in patients with overt congestive failure.
Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blockers can precipitate cardiac failure. At the first signs or symptoms of heart failure, discontinuation of ZIAC should be considered.
Abrupt Cessation of Therapy: Abrupt cessation of beta-blockers should be avoided. Even in patients without overt coronary artery disease, it may be advisable to taper therapy with ZIAC over approximately 1 week with the patient under careful observation. If withdrawal symptoms occur, beta-blocking agent therapy should be reinstituted, at least temporarily.
Peripheral Vascular Disease: Beta-blockers should be used with caution in patients with peripheral vascular disease.
Bronchospastic Disease: PATIENTS WITH BRONCHOSPASTIC PULMONARY DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS.
Anesthesia and Major Surgery: If used perioperatively, particular care should be taken when anesthetic agents that depress myocardial function, such as ether, cyclopropane, and trichloroethylene, are used.
Diabetes and Hypoglycemia: Beta-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents, should be cautioned. Also, latent diabetes mellitus may become manifest and diabetic patients given thiazides may require adjustment of their insulin dose.
Thyrotoxicosis: Beta-adrenergic blockade may mask clinical signs of hyperthyroidism. Abrupt withdrawal of beta-blockade may be followed by an exacerbation of the symptoms of hyperthyroidism or may precipitate thyroid storm.
Renal Disease: Cumulative effects of the thiazides may develop in patients with impaired renal function. In such patients, thiazides may precipitate azotemia. In subjects with creatinine clearance less than 40 mL/min, the plasma half-life of bisoprolol fumarate is increased up to threefold, as compared to healthy subjects.
Hepatic Disease: ZIAC should be used with caution in patients with impaired hepatic function or progressive liver disease.

PRECAUTIONS

General: *Electrolyte and Fluid Balance Status:* Periodic determination of serum electrolytes should be performed, and patients should be observed for signs of fluid or electrolyte disturbances. Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Hypokalemia may develop. Hypokalemia and hypomagnesemia can provoke ventricular arrhythmias or sensitize or exaggerate the response of the heart to the toxic effects of digitalis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than salt administration, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Parathyroid Disease: Calcium excretion is decreased by thiazides, and pathologic changes in the parathyroid glands, with hypercalcemia and hypophosphatemia, have been observed in a few patients on prolonged thiazide therapy.

Hyperuricemia: Hyperuricemia or acute gout may be precipitated in certain patients receiving thiazide diuretics. Bisoprolol fumarate, alone or in combination with HCTZ, has been associated with increases in uric acid.
Drug Interactions: ZIAC may potentiate the action of other antihypertensive agents used concomitantly. ZIAC should not be combined with other beta-blocking agents. In patients receiving concurrent therapy with clonidine, if therapy is to be discontinued, it is suggested that ZIAC be discontinued for several days before the withdrawal of clonidine.

ZIAC should be used with caution when myocardial depressants or inhibitors of AV conduction or antiarrhythmic agents are used concurrently.

Bisoprolol Fumarate: Concurrent use of rifampin increases the metabolic clearance of bisoprolol fumarate, shortening its elimination half-life. Pharmacokinetic studies document no clinically relevant interactions with other agents given concomitantly, including thiazide diuretics, digoxin and cimetidine. There was no effect of bisoprolol fumarate on prothrombin times in patients on stable doses of warfarin.

Risk of Anaphylactic Reaction: While taking beta-blockers, patients with a history of severe anaphylactic reaction may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic and may be unresponsive to the usual doses of epinephrine used to treat allergic reactions.

Hydrochlorothiazide: The following drugs may interact with thiazide diuretics. Alcohol, barbiturates, or narcotics–potentiation of orthostatic hypotension may occur. Dosage adjustment of the antidiabetic drugs (oral agents and insulin) may be required. Other antihypertensive drugs–additive effect or potentiation. Cholestyramine and colestipol resins–single doses of cholestyramine and colestipol resins bind the hydrochlorothiazide and reduce its absorption in the gastrointestinal tract by up to 85 percent and 43 percent, respectively. Corticosteroids, ACTH –intensified electrolyte depletion, particularly hypokalemia. Possible decreased response to pressor amines but not sufficient to preclude their use. Possible increased responsiveness to muscle relaxants, nondepolarizing. Generally, lithium should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. The administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics.

In patients receiving thiazides, sensitivity reactions may occur with or without a history of allergy or bronchial asthma. Photosensitivity reactions and possible exacerbation or activation of systemic lupus erythematosus have been reported in patients receiving thiazides. The antihypertensive effects of thiazides may be enhanced in the post-sympathectomy patient.
Laboratory Test Interactions: Based on reports involving thiazides, ZIAC may decrease serum levels of protein-bound iodine without signs of thyroid disturbance. Because it includes a thiazide, ZIAC should be discontinued before carrying out tests for parathyroid function (see **PRECAUTIONS**–*Parathyroid Disease*).

ADVERSE REACTIONS

ZIAC: Bisoprolol fumarate/H6.25 mg is well tolerated in most patients. Most adverse effects (AEs) have been mild and transient. In more than 65,000 patients treated worldwide with bisoprolol fumarate, occurrences of bronchospasm have been rare. Discontinuation rates for AEs were similar for B/H6.25 mg and placebo-treated patients.

In the United States, 252 patients received bisoprolol fumarate (2.5, 5, 10, or 40 mg)/H6.25 mg and 144 patients received placebo in two controlled trials. In Study 1, bisoprolol fumarate 5/H6.25 mg was administered for 4 weeks. In Study 2, bisoprolol fumarate 2.5, 10 or 40/H6.25 mg was administered for 12 weeks. All adverse experiences, whether drug-related or not, and drug-related adverse experiences in patients treated with B2.5-10/H6.25 mg, reported during comparable, 4 week treatment periods by at least 2% of bisoprolol fumarate/H6.25 mg-treated patients (plus additional selected adverse experiences) are presented in the following table:

ZIAC® (Bisoprolol Fumarate and Hydrochlorothiazide) Tablets

Body System/ Adverse Experience	% of Patients with Adverse Experiences*			
	All Adverse Experiences		Drug-Related Adverse Experiences	
	Placebo†	B2.5-40/H6.25†	Placebo†	B2.5-10/H6.25†
	(n=144) %	(n=252) %	(n=144) %	(n=221) %
Cardiovascular				
bradycardia	0.7	1.1	0.7	0.9
arrhythmia	1.4	0.4	0.0	0.0
peripheral ischemia	0.9	0.7	0.9	0.4
chest pain	0.7	1.8	0.7	0.9
Respiratory				
bronchospasm	0.0	0.0	0.0	0.0
cough	1.0	2.2	0.7	1.5
rhinitis	2.0	0.7	0.7	0.9
URI	2.3	2.1	0.0	0.0
Body as a Whole				
asthenia	0.0	0.0	0.0	0.0
fatigue	2.7	4.6	1.7	3.0
peripheral edema	0.7	1.1	0.7	0.9
Central Nervous System				
dizziness	1.8	5.1	1.8	3.2
headache	4.7	4.5	2.7	0.4
Musculoskeletal				
muscle cramps	0.7	1.2	0.7	1.1
myalgia	1.4	2.4	0.0	0.0
Psychiatric				
insomnia	2.4	1.1	2.0	1.2
somnolence	0.7	1.1	0.7	0.9
loss of libido	1.2	0.4	1.2	0.4
impotence	0.7	1.1	0.7	1.1
Gastrointestinal				
diarrhea	1.4	4.3	1.2	1.1
nausea	0.9	1.1	0.9	0.9
dyspepsia	0.7	1.2	0.7	0.9

*Averages adjusted to combine across studies.
†Combined across studies.

Other adverse experiences that have been reported with the individual components are listed below.
Bisoprolol Fumarate: In clinical trials worldwide, a variety of other AEs, in addition to those listed above, have been reported. While in many cases it is not known whether a causal relationship exists between bisoprolol and these AEs, they are listed to alert the physician to a possible relationship. *Central Nervous System:* Unsteadiness, vertigo, syncope, paresthesia, hyperesthesia, sleep disturbance/vivid dreams, depression, anxiety/restlessness, decreased concentration/memory. *Cardiovascular:* Palpitations and other rhythm disturbances, cold extremities, claudication, hypotension, orthostatic hypotension, chest pain, congestive heart failure. *Gastrointestinal:* Gastric/epigastric/abdominal pain, peptic ulcer, gastritis, vomiting, constipation, dry mouth. *Musculoskeletal:* Arthralgia, muscle/joint pain, back/neck pain, twitching/tremor. *Skin:* Rash, acne, eczema, psoriasis, skin irritation, pruritus, purpura, flushing, sweating, alopecia, dermatitis, exfoliative dermatitis (very rarely), cutaneous vasculitis. *Special Senses:* Visual disturbances, ocular pain/pressure, abnormal lacrimation, tinnitus, decreased hearing, earache, taste abnormalities. *Metabolic:* Gout. *Respiratory:* Asthma, bronchitis, dyspnea, pharyngitis, sinusitis. *Genitourinary:* Peyronie's disease (very rarely), cystitis, renal colic, polyuria. *General:* Malaise, edema, weight gain, angioedema.

In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents and should be considered potential adverse effects: *Central Nervous System:* Reversible mental depression progressing to catatonia, hallucinations, an acute reversible syndrome characterized by disorientation to time and place, emotional lability, slightly clouded sensorium. *Allergic:* Fever, combined with aching and sore throat, laryngospasm, and respiratory distress. *Hematologic:* Agranulocytosis, thrombocytopenia. *Gastrointestinal:* Mesenteric arterial thrombosis and ischemic colitis. *Miscellaneous:* The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with bisoprolol fumarate during investigational use or extensive foreign marketing experience.
Hydrochlorothiazide: The following adverse experiences, in addition to those listed in the above table, have been reported with hydrochlorothiazide (generally with doses of 25 mg or greater). *General:* Weakness. *Central Nervous System:* Vertigo, paresthesia, restlessness. *Cardiovascular:* Orthostatic hypotension (may be potentiated by alcohol, barbiturates, or narcotics). *Gastrointestinal:* Anorexia, gastric irritation, cramping, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, cholecystitis, sialadenitis, dry mouth. *Musculoskeletal:* Muscle spasm. *Hypersensitive Reactions:* Purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions. *Special Senses:* Transient blurred vision, xanthopsia. *Metabolic:* Gout. *Genitourinary:* Sexual dysfunction, renal failure, renal dysfunction, interstitial nephritis.

LABORATORY ABNORMALITIES

ZIAC: Because of the low dose of hydrochlorothiazide in ZIAC, adverse metabolic effects with B/H6.25 mg are less frequent and of smaller magnitude than with HCTZ 25 mg.

Treatment with both beta-blockers and thiazide diuretics is associated with increases in uric acid. Mean increases in serum triglycerides were observed in patients treated with bisoprolol fumarate and hydrochlorothiazide 6.25 mg. Total cholesterol was generally unaffected, but small decreases in HDL cholesterol were noted.

Other laboratory abnormalities that have been reported with the individual components are listed below.
Bisoprolol Fumarate: In clinical trials, the most frequently reported laboratory change was an increase in serum triglycerides, but this was not a consistent finding.

Sporadic liver test abnormalities have been reported. In the U.S. controlled trials experience with bisoprolol fumarate treatment for 4 to 12 weeks, the incidence of concomitant elevations in SGOT and SGPT of between 1 to 2 times normal was 3.9%, compared to 2.5% for placebo. No patient had concomitant elevations greater than twice normal.

In the long-term, uncontrolled experience with bisoprolol fumarate treatment for 6 to 18 months, the incidence of one or more concomitant elevations in SGOT and SGPT of between 1-2 times normal was 6.2%. The incidence of multiple occurrence was 1.9%. For concomitant elevations in SGOT and SGPT of greater than twice normal, the incidence was 1.5%. The incidence of multiple occurrences was 0.3%. In many cases these elevations were attributed to underlying disorders, or resolved during continued treatment with bisoprolol fumarate.

Other laboratory changes included small increases in uric acid, creatinine, BUN, serum potassium, glucose, and phosphorus and decreases in WBC and platelets. There have been occasional reports of eosinophilia. These were generally not of clinical importance and rarely resulted in discontinuation of bisoprolol fumarate.

As with other beta-blockers, ANA conversions have also been reported on bisoprolol fumarate. About 15% of patients in long-term studies converted to a positive titer, although about one-third of these patients subsequently reconverted to a negative titer while on continued therapy.
Hydrochlorothiazide: Hyperglycemia, glycosuria, hyperuricemia, hypokalemia and other electrolyte imbalances (see **PRECAUTIONS**), hyperlipidemia, hypercalcemia, leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, and hemolytic anemia have been associated with HCTZ therapy.

See **DOSAGE AND ADMINISTRATION** section in package insert for complete dosing and precautionary information.



LEDERLE PHARMACEUTICAL DIVISION
American Cyanamid Company
Wayne, New Jersey 07470

Under license of E. MERCK
Darmstadt, Germany

CI 4567-3
Revised June 12, 1997



LEDERLE PHARMACEUTICAL DIVISION
American Cyanamid Company
Wayne, New Jersey 07470



67081-00

Reporte de Casos:

Sudden Periodic Paralysis: rare manifestation of thyrotoxicosis

José Ramírez Rivera MD FACP* and Axel D. Flores MD**

Abstract: *Nonfamilial hypokalemic thyrotoxic periodic paralysis is rarely diagnosed among Caucasians and blacks in the western world but it is relatively common among Asiatics. Sudden paralysis occurring while at rest after a large carbohydrate meal or strenuous exercise in an undiagnosed mild thyrotoxic patient is a common presentation.*

A case illustrating such presentation is reported. Intracellular shifts of potassium triggered or facilitated by hyperthyroidism and hyperinsulinemia are the biochemical features. Correction of the thyrotoxic state is the definitive treatment for this disorder. Judicious administration of potassium is indicated during the hypokalemic episode to prevent life-threatening arrhythmias.

Key words: Periodic paralysis, hypokalemia, thyrotoxicosis, Puerto Ricans, Hispanic.

INTRODUCTION

Hypokalemic periodic paralysis is seldom seen as a complication of hyperthyroidism in the Western World. It has been reported in 4.3 percent of male and .04 per cent of female thyrotoxic patients in Japan (1) and in 1.8 per cent of hyperthyroid patients in a southern Chinese population (2). Although prevalent in other Asian countries, it is rarely observed in Caucasians and blacks (3,4).

The clinical features of thyrotoxic periodic paralysis are so specific that the diagnosis can be made on the basis of its clinical presentation. However, even when life-threatening complications of hypokalemia are present, the diagnosis may be overlooked: sudden paralysis frequently presents in context with minimally symptomatic thyrotoxicosis; the association of hypokalemic paralysis with thyrotoxicosis is totally unfamiliar to most western clinicians.

We present here a case in which sudden flaccid paralysis of all extremities was the presenting sign of thyrotoxic periodic paralysis.

Case Report

A healthy 32 year old Puerto Rican policeman was brought to the emergency room shortly after he awoke unable to move his upper and lower extremities. On retrospect, he had experienced occasional cramps and weakness in his legs since two months ago. He acknowledged occasional palpitations, vague heat intolerance, tiredness and increased appetite, but no recent weight loss. No one in his family had suffered from thyroid disease or a sudden onset of paralysis. His last meal, four hours previous to admission, consisted of a generous serving of lasagna and a milk shake. He took no medicines, smoked 10 cigarettes daily for the last 14 years and drank 4-5 beers on weekends.

On admission, the temperature was 36.4° C, the pulse 125 beats per minute, and the blood pressure 150/70 mmHG. He was alert and oriented; he was anxious about his paralysis but in no other distress. The skin was warm and moist. Lid lag was present but there was no proptosis. The thyroid gland was firm and symmetrically enlarged but there were no other cervical masses. The lungs were clear. Cardiac rhythm was regular and there were no murmurs. There was a flaccid paralysis of all extremities. Deep tendon reflexes were absent throughout. The cranial nerves and sensory examination were normal.

The electrocardiogram on admission showed a rate of 123 beats per minute. There were reporalization abnormalities of uncertain origin (Fig. 1A). The Q wave was broad and the corrected Q-T internal was 0.5 seconds, most probably representing a prolonged Q-U. The potassium on admission was 1.5mEq/L, the glucose was 156 mg/dl. The sodium, chloride, bicarbonate, magnesium, blood urea, nitrogen and creatinine, were within normal limits.

From the Department of Internal Medicine of the Hospital de la Concepción, San Germán, Puerto Rico
Address correspondence to: José Ramírez Rivera, MD - Caparra Heights, 700 Eucalipto, San Juan, PR 00920
** Director of Clinical Investigation, Department of Medicine, Hospital de la Concepción. Professor of Medicine, University of Puerto Rico School of Medicine.*
*** Chief Resident Department of Medicine, Hospital de la Concepción.*

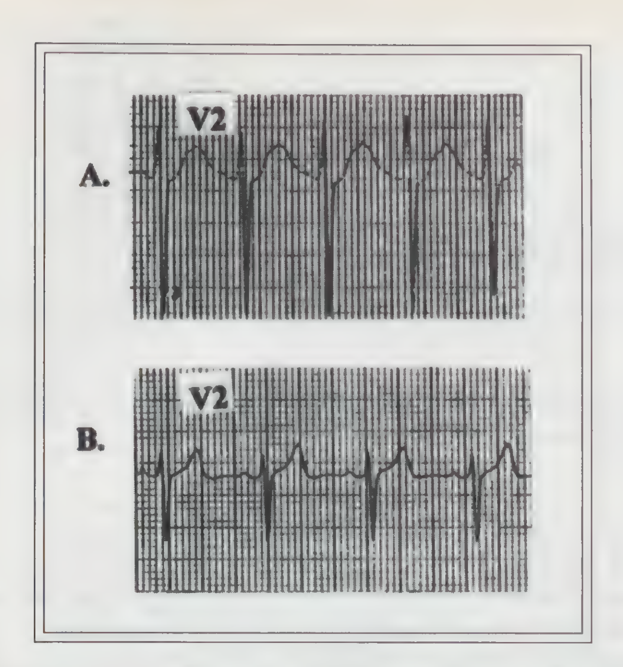


Fig. 1 A. EKG on admission, lead V2, showing the prolonged Q-U interval.
B. EKG seven hours after admission, lead V2, showing a normal tracing.

Intravenous potassium was initiated. After 4 hours and 90mEq of potassium muscular strength and reflexes fully recovered. Seven hours after admission, the electrocardiogram was within normal limits (Fig.1B). His potassium levels improved and remained normal. The next day, T3 uptake was 43.6%, T4 14.6 ug/dL and TSH was less than <0.05 IU/ml. Four days after admission a 24 hour thyroid uptake was 63.8% (N: 10-30%); a scan was suggestive of a diffuse toxic goiter.

Fasting insulin concentration was 106/2 u U/ml (N: <20) and the glucose was 97mg/dl. During a glucose tolerance test, hyperinsulinemia persisted but there was no hyperglycemia and potassium levels remained within normal limits.

Tapazole 10mg and propranolol 10mg three times a day were initiated with effective control of symptoms. The patient was discharged asymptomatic five days after admission. When last seen 13 months later, he was still taking tapazole daily, was euthyroid, and had had no recurrence of the paralysis.

Discussion

Hypokalemic periodic paralysis is a rare complication of hyperthyroidism. Nearly 90% of reported cases have occurred in oriental patients (1,2). There is a male predominance. It is 6 to 20 times more common in men than in women. The incidence in the United States is one tenth of that in Asian countries. Hispanics are 15% of USA cases reported (5, 6). The first paralytic episode usually occurs shortly after the onset of thyrotoxic symptoms which at times go unnoticed. Characteristically, the episodes occur in the early morning after strenuous exercise or a high carbohydrate meal.

The paralysis is acute, of variable intensity and duration and predominantly involves the lower extremities. It is usually flaccid and symmetrical, but may be asymmetrical. Proximal muscles are affected more severely than distal muscles, bulbar, ocular and respiratory muscles are almost never involved. When the paralysis is asymmetrical, muscles most severely exercised before the attack are the most affected. The mental and sensory functions are spared. Deep tendon reflexes are often markedly diminished or absent (3). Attacks may resolve spontaneously and leave no residual weakness

Hypokalemia in the presence of hyperthyroidism is the hallmark of this syndrome. Hyperinsulinemia is also frequently present. Electrocardiographic findings during paralytic episodes are those described in hypokalemia; they include the appearance of a U wave, T wave flattening, ST segment depression or QT prolongation; paroxysmal suproventricular tachycardia may occur and ventricular fibrillation has been reported (8). There may also be 1st or 2nd degree A-V block. Electromyographic studies show an increased amplitude of action potentials during prolonged exercise followed by a greater decrease in amplitude after exercise (5). Electromyographic studies after the euthyroid state is achieved are normal.

The mechanism by which hyperthyroidism produces hypokalemia has been studied. The diminished serum potassium concentration does not represent a deficiency in total body potassium. There is a shift of K+ intracellularly mediated by an increased Na^+-K^+-AT Pase activity in skeletal muscle, lungs and kidneys (9). Hyperinsulinemia and androgen also activate the Na^+-K^+-AT Pase pump. This may explain the relationship of paralytic attacks to heavy carbohydrate loads, glucose/insulin challenges and the male preponderance of this syndrome (2). Hypokalemia may not be the sole cause of the neuromuscular problems. Ultrastructural studies of muscle, in susceptible patients, show proliferation and dilatation of the sarcoplasmic reticulum (10).

The definitive treatment for thyrotoxic periodic paralysis is the correction of the hyperthyroid state. Once the euthyroid state is achieved the episodes of paralysis cease (2, 5, 6). Prophylactic potassium does not prevent recurrence of attacks but propranolol is known to decrease frequency and attenuate severity of paralytic episodes.

For the acute attack, oral potassium replacement is the preferred treatment. The following empirical protocol has been recommended (6): 27mEq potassium every 2 hours until muscle strength begins to recover, then every four hours until full recovery. There has not been any good documentation that intravenous treatment is advantageous, nevertheless, it is frequently used. It is important to monitor serum K^+ closely. During recovery phase K^+ shifts out of the cells and aggressive replacement may result in hyperkalemia.

Although thyrotoxic periodic paralysis and familial periodic paralysis have identical biochemical and clinical presentations, they are not the same disease. Most patients with familial paralysis are Caucasians (3) while thyrotoxic paralysis is most prevalent among Asians (1). Familial paralysis has an autosomal dominant transmission and symptoms appear frequently before age 20 while thyrotoxic paralysis parallels the usual time of presentation of hyperthyroidism, the second and third decade. Both forms of periodic paralysis affect predominantly males. But the male to female ratio is much greater in thyrotoxic paralysis. It is 12:1 versus 3:1. A determining difference is that thyrotoxic paralysis can be induced only in the context of hyperthyroidism (2, 3). It does not occur when patients are euthyroid, but will recur if hyperthyroidism redevelops. Patients with familial periodic paralysis, on the contrary, are usually euthyroid. A challenge with exogenous thyroid will not increase the frequency or severity of their symptoms.

REFERENCES

1. Shizume K, Shishiba Y, Kuma K, Noguchi S, Tahiti J, Ito K, Noh JY. Comparison of the incidence of association of periodic paralysis and hyperthyroidism in Japan 1957 and 1991. Endocrinol - Jpn 1992; 39:315-318.
2. McFadzean AJS, Yeung R. Periodic paralysis complicating thyrotoxicosis in Chinese. Br Med J. 1969; 1:760.
3. Yeo PP, O'Neill WC. Thyrotoxicosis and periodic paralysis. Medical Grand Rounds 1984; 3:10-25.
4. Hochberg DA, Vassolo M, Paniagua D., Thyrotoxic periodic paralysis in a black man. South Med J 1996; 89:735-737.
5. Kelley DE, Gharib H, Kennedy FP, Duda RJ Jr., Mc Mannis PG Thyrotoxic periodic paralysis. Report of 10 cases and review of electromyographic findings, Arch Intern Med 1989; 149: 2597-2600.
6. Ober KP. Thyrotoxic periodic paralysis in the United States. Report of 7 cases and review of the literature, Medicine 1992; 71: 109-120.
7. Miller JD, Quillian W, Cleveland WW. Nonfamilial hypokalemic periodic paralysis and thyrotoxicosis in a 16 year old male. Pediatrics 1997; 100:412-414.
8. Fisher J. Thyrotoxic periodic paralysis with ventricular fibrillation. Arch Intern Med 1982; 142:1362-1364.
9. Kubota K, Ingbar SH, Influences of thyroid status and sympathoadrenal system on external potassium disposal. Am J Physiol 1990; 258: E 428-435.
10. Engel AG. Electron microscopic observations in primary hypokalemic and thyrotoxic periodic paralysis. Mayo Clinic Proc 1966; 41:798-808.
11. Tinker TD, Vanalta JB. Thyrotoxic hypokalemic periodic paralysis: Report of four cases and review of the literature. J Okla State Med Assoc 1987; 80: 76-83.

Vol. 90 • 4 - 5 - 6 / 1998 • Pág. 91, 92

Reporte de Casos:

Solid and Papillary Neoplasm of the Pancreas: A case presentation

Margarita Rivera, M.D., Víctor N. Ortiz, M.D., FACS, FAAP; Normando Durán, M.D., Oscar Trujillo, M.D.

***Summary:** Solid and papillary tumors of the pancreas are very rare malignancies, more commonly occurring in young women. They usually present as asymptomatic, large abdominal masses, and different from the most common neoplasm of the pancreas, which is the adenocarcinoma, these tumors have a high percentage of curability when treated by complete surgical resection.(6) For this reason, when the diagnosis of Frantz's tumor is made or strongly suspected, every attempt should be made for complete surgical excision since curability is high and radiotherapy and, or chemotherapy are of no use for its treatment.*

Introduction

Solid and papillary neoplasms of the pancreas are very rare malignancies when compared to the most common adenocarcinoma, arising from the main pancreatic duct or exocrine pancreas. It is a tumor generally occuring in young women but with the peculiarity of a very low grade malignancy and a high incidence of curability by complete surgical excision.

The purpose of this presentation is to document the case of a 13 years old girl who presented with fever and right upper quadrant abdominal pain, associated to a head of pancreas mass on CT scan. The patient underwent surgery and was found with a solid and papillary tumor of the pancreas, for which a Whipple's procedure or pancreticoduodenectomy was performed. The girl has been followed for approximately one and half years without evidence of recurrence of her disease.

Case Report

A 13 years old girl without history of previous disease was taken to Bella Vista emergency room on January 1996 due to abdominal pain associated with fever and vomiting of one day of duration. On physical exam the patient showed right upper quadrant abdominal pain radiating to the right flank. Initial laboratories evidenced leukocytosis with shift to the left and a normal urinalysis as well as normal bilirubin and alkaline phosphatase levels. An upper abdominal sonogram visualized a normal gallbladder but a large mass underneath the liver. A CT scan of the abdomen and pelvis revealed a solid mass of the head of the pancreas with dilatation of the common bile duct. (Fig. 1)

The patient was taken to the operating room and a right subcostal incision was done. A perforated appendicitis with a localized abscess was found in the right paracolic gutter. By exploration a large mass of the head of the pancreas was confirmed with dilatation of the common bile duct and no evidence of liver lesions. Appendectomy and abscess drainage were performed, folowed by a pancreaticoduodenectomy or Whipple's procedure. The portion of the tumor extending to the superior mesenteric vein at it's posterior wall could not be completely resected so a small rim of tumor was left attached to it. After recovery from the surgical procedure and with the pathologic diagnosis of solid and papillary or Frantz's tumor of the pancreas, the patient underwent a second exploration four months later. In this second exploration specimens from the tissues surrounding the superior mesenteric vein, portal vein, aortocaval area, and inferior margin of resection were submitted for pathological evaluation and no tumor was found in either specimens. At present the patient has been followed for approximately one and a half years and there is no evidence of local recurrence of malignancy nor distant metastases.

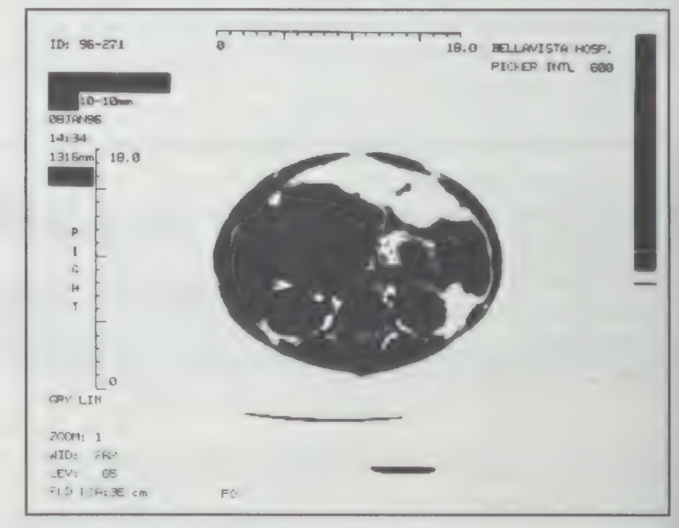


Fig. 1. CT scan showing a large head of the pancreas tumor, solid tumor with some mall hypodense foci.

Department of Surgery, Bella Vista Hospital and Department of Surgery, Mayaguez Medical Center, Mayaguez, P.R.

Discussion

Solid and papillary tumors of the pancreas, also known as Frantz's tumors since he first described in 1959, is a very rare malignancy, most commonly found in young women.(1) They usually present as a large abdominal mass, mostly asymptomatic or with acute onset of abdominal pain associated to tumor necrosis or rupture. These tumors are more common in the body and tail of the pancreas, as in the case presented here. Frantz's tumor is almost always localized, well encapsulated lesion with very low incidence of metastases in which cure is highly accesible by complete surgical resection.(2) Even when the infrequent metastases of the tumor to the liver and lung are found, the combination of complete resection of all macroscopic disease and of the metastases results in an excellent long term survival.(1)

The imaging studies giving the most characteristic features of Frantz's tumors are the sonogram and the CT scan. Solid and papillary tumors of the pancreas usually appear as well localized, well encapsulated lesions with solid and cystic areas, where cystic portions tend to correlate with tumor necrosis. These tumors are almost always poorly vascularized and with areas of calcification.(1,2)

The most important histologic characteristic of this tumor is the solid and papillary epithelial pattern in which cytology reveals small, uniform cells with an eosinophilic cytoplasm and round nuclei. The findings of highly malignant tumors are: nuclear atypia, pleomorphism, and abundant mitosis, however, these are rarely present even in the metastatic lesions.(3) (Figures 2 and 3)

In the case of patient presented, even when a small rim of tumor was left attached to the superior mesentric vein during the first operation, there was no evidence of residual tumor in the second surgical intervention. Since these tumors are poorly vascularized lesions, the absence of residual tumor evidenced at her second surgery may have been the extensive devascularization of the small amount of tumor left unresected at her initial surgey.



Fig. 2. At low power the tumor shows pseudopapillary processes and the lining cells appear relatively uniform.

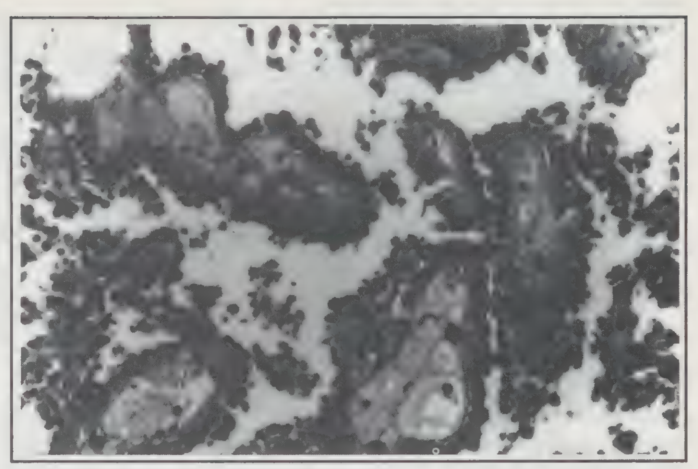


Fig. 3. A closer view shows the uniformity of the epithelial cells that are polygonal with round to oval vesicular nuclei.

However, because Frantz's tumors can show local recurrence many years after diagnosis and resection, it is important to follow the patient with CT scan yearly.(4) It is important to realize that, since patients diagnosed with solid and papillary tumors of the pancreas have great chances of cure by complete surgical resection, extensive surgical procedures like pancreatectomy and Whipple procedure, as in this case, should be performed when the size, position, or extension of the tumor make them necessary, assuming that the patient's condition is good enough to tolerate the procedure.

Resumen: *Los tumores sólidos y papilares del páncreas son malignidades muy raras, presentándose mayormente en mujeres jóvenes. Usualmente se presentan como masas abdominales grandes y asintomáticas y, a diferencia del neoplasma más común del páncreas, el adenocarcinoma, estos tumores tienen un gran porciento de curabilidad cuando son tratados mediante resección quirúrgica complete.(6) Por esta razón, cuando el diagnóstico de tumor de Frantz's se realiza o se sospecha fuertemente, todo intento de resección completa se debe realizar ya que el mismo no responde bien a radioterapia ni a quimioterapia.*

Referencres

1. Tait N., Greenberg M.L., Osborn R.A., Little J.M. Frantz's tumor: papillary and cystic carinoma of the pancreas. Aust NZJ Surg 1995; 65:237-241.
2. Zinner M.J. Solid and papillary neoplasms of the pancreas. Surgical clinics of North America 1995; 75:1017-1024
3. González R., Ríos J.J., Villar J.L., et al. Papillary cystic neoplasm of the pancreas with liver metastases coexisting with thyroid papillary carcinoma. Arch Pathol Lab Med 1995; 119:268-273.
4. Whittle C., Ferreira R., Franco C., Schiappacsse V. Papillary cystic tumor of pancreas: report of one case. Rev Med Chile 1994; 122:815-818.
5. Grieshop N., Wiebke E., Kratzer S., Madura J. Cystic neoplasm of the pancreas. Am Surg 1994; 60:509-515.
6. Jeng L.B., Chen M.F., Tang R.P. Solid and papillary neoplasm of the pancreas: Emphasis on surgical treatment. Arch Surg 1993; 128:433-436.

Reporte de Casos:

Bifid Scrotum, Perineal Hamartoma and High Imperforate Anus: A Case Report

DAVID H. VILLARREAL MD. ***; VICTOR N. ORTIZ MD. FACS. FAAP *
JUAN R. ITURREGUI MD. FACS. **; GISELLE SUAREZ MD. ***; NORMANDO DURAN MD. ***

Summary: *This is a case report of a newborn patient with imperforate anus, urethro-colonic fistula, perianal hamartoma, and bifid scrotum. Successful staged repair of these anomalies is described together with review of the embriology related to the case.*

INTRODUCTION

Clinical studies have shown the association of genitourinary anomalies with imperforate anus. The mnemonic VACTER or VACTERL (vertebral defects, anal atresia, cardiac, tracheo-esophageal, renal and limb anomalies) includes other defects, besides genitourinary anomalies that are frequently associated with imperforate anus. These anomalies can be explained by developmental changes in early fetal life. Urogenital tract abnormalities are common and no portion can be excluded of a possible malformation. We report a case of high imperforate anus associated with a perineal hamartoma and bifid scrotum, along with its successful staged repair.

CASE REPORT

A 3.3 kg. male newborn was delivered by cesarean section at term. Prenatal history included third trimester maternal pre-eclampsia without significant medical problems, no medications during the first trimester and no known exposure to infectious diseases was present. Physical examination of the newborn revealed imperforate anus and anomalies of the external genitalia.

The right and left scrotal sacs were not fused and there was a large diverticulum arising between the sacs covered by scrotal skin. Its base was located in the perineal area. No recto-perineal fistula was found (fig. 1)

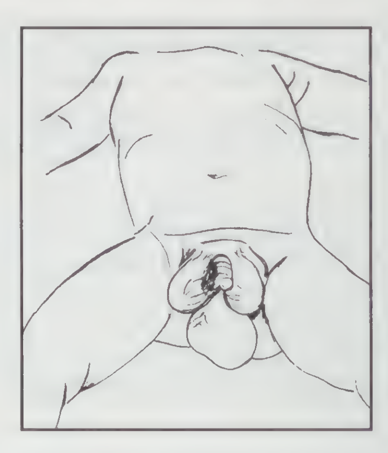


Figure 1. Bifid scrotum and perianal diverticulum

A right transverse colostomy was performed one day after birth. The patient was discharged from the hospital to await surgical reconstuction of rectum, anus and genitalia. Voiding cystourethrogram and distal gastrographin enema were done revealing a grade two vesicoureteral reflux and high imperforate anus with a recto-urethral fistula. The patient was hospitalized for staged reconstruction at 10 months of age. The imperforate anus was repaired using a posterior sagittal anorectoplasty as described by PeÒa and De Vries.(1) During the procedure a fistulous tract to the urethra was transected and closed transversely. Finally, a suprapubic cystostomy was done to protect the urethroplasty.

A third procedure was performed one month later, consisting in repair of the external genitalia. An incision between both hemiscrotum was done. Multiple attachments contibuting to the chordee were relieved and the hidden penis was straightened up with skin dissection until adequate length was obtained. The diverticulum like structure was excised, pathologic report demonstrated it to be a hamartoma.

DISCUSSION

Imperforate anus is associated to a wide variety of urogenital abnormalities. A review of the development of rectum, anus, urinary tract and genitalia is helpful to understand the etiology of these malformations.(2)

The cloaca forms the terminal blind-ending portion of the hindgut. From the cloaca, at about the thirteenth

*From the Department of Surgery, Mayaguez Medical Center, Division of: *Pediatric Surgery; **Urology; ***General Surgery*
All correspondence should be addressed to: Dr. Victor N. Ortiz, Box 3008, Mayaguez, PR 00681

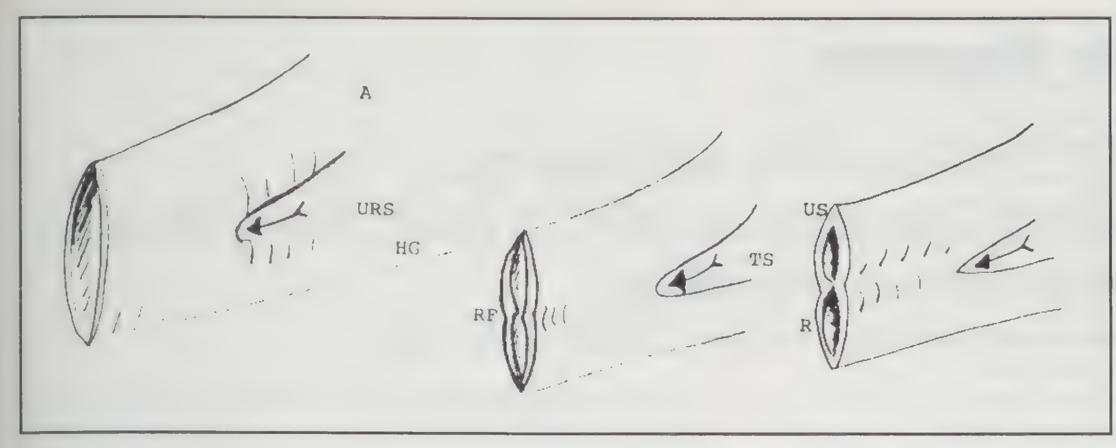


Figure 2.
(I) Subdivision of cloaca: urorectal septum (URS) proceeds externally to separate the allantois (A) and the hindgut (HG).
(II) Lateral ridges of mesenchymal tissue, Rathke's folds (RF), fuse with the superior portion of the urorectal septum, Tourneaux's spur (TS), to separate cloaca
(III) finally into anterior urogenital sinus (UG) and rectum (R).

day a ventral diverticulum develops, the allantois. In the five week embryo the allantois expands to form the early bladder. It receives the wolffian ducts and migrates caudally towards the exterior as the urogenital sinus. At this point the urogenital sinus has extensive communications with the hindgut. The urorectal septum separates the urogenital sinus from the hindgut (fig. 2) This septum has two portions. The caudal portion is a fold of mesenchymal tissue (Tourneauxís spur) that grows caudally. Lateral ingrowth of mesenchymal tissue (Rathkeís fold) complete the urorectal septum. Defects in the formation of this septum create a wide variety of fistulas between the urinary and intestinal tracts.

Imperforate anus is classified as high or low depending upon where the rectum ends in relation to the levator ani muscle complex (old classification of Douglas, Stephens and Smith),(3) In the great majority of cases the rectum ends in a fistula. In males with high imperforate anus the fistula usually communicates with the prostatic urethra. In females it usually communicates with the interposed upper vagina. The low lying imperforate anus presents fistulous tracts to the perineum. In males this is seen in the median raphe, scrotum or penis. In the female it is seen at the posterior fourchette and the caudal portion of the vagina.

Inadequate migration of the urorectal septum in early fetal life results in the formation of imperforate anus, bifid scrotum, and urethra-rectal fistula. Curiously, these anomalies were accompanied by a hamartoma. This phenomenon has not been described associated to the malformations of imperforate anus and bifid scrotum. Even though we have no embryologic basis to explain the above anomalies so as to categorically state this is a new syndrome; we must watch for more future reports in which these anomalies might come together. Further embryologic studies will then be needed to explain their presence.

In summary, we report a case of high imperforate anus, uretro-rectal fistula, perineal hamartoma and bifid scrotum, and the successful staged repair of these anomalies, with review of the embryology.

Resumen: *En este articulo reportamos el caso de un paciente nacido con ano imperforado, fistula recto-uretral, escroto bifido y un hamartoma perineal. Describimos la reparacion de estos defectos y revisamos la embriologia relacionada con los mismos.*

BIBLIOGRAPHY

1. Hoekstra W.J., Scholtmeijer R.J., Molenar J.C., and Schroeder F.H.: Urogenital tract abnormalities associated with congenital anorectal anomalies: J. Urol. 1983 13:962-963.

2. Pena A., DeVries P.A.: Posterior sagital anorectoplasty: important technical considerations and new applications J. Ped surg. 1982 17:796-881.

3. Thompson I.M., Hooks C.A.: The urologic significance of the imperforate anus Amer surg. 1956 22: 1112-1115.

4. Miller S.F., Transposition of external genitalia associated with the syndrome of caudal regression J. Urol. 1972 108: 818-822.

5. Lage J.M., Driscoll S.G., Bieber F.R.: Transposition of the external genitalia associated with the caudal regression syndrome J. Urol. 1987 138: 387-389.

6. Kaneti J., Sober I., Barki Y.: Congenital anterior diverticulum Eur Urol. 1984 10: 48-52.

7. Sweetzer T.H.: Congenital urethral diverticula in a male patient J Urol. 1967 97: 93-97.

Artículos de Repaso:

Acute Spinal Cord and Head Injury: Case Report and Discussion of Cardiac, Respiratory and Endocrine Abnormalities

Treatment With Temporary Transvenous Cardiac Pacing

Charles D. Johnson, M.D., F.A.C.C.; Ramon M. Perea López, M.D.
Luis Rodríguez, M.D.

Abstract: *We report a male patient who after a fall suffered high cervical spinal cord and head (cerebral) injuries. These injuries led to spinal shock, marked sinus bradycardia and asystolic cardiac and respiratory arrests, recalcitrant central traumatic diabetes insipidus, and death within approximately seven weeks. Temporary transvenous cardiac pacing proved useful in the management of this patient.*

Key Words: *Cardiorespiratory Abnormalities, Diabetes Insipidus, Spinal Cord Injury, Head Trauma, Cardiac Pacing*

INTRODUCTION

Cardiovascular abnormalities may complicate acute spinal cord injuries, especially severe high cervical spinal cord injuries. These problems consist of spinal shock, hypotension, cardiac arrhythmias, both bradyarrhythmias such as severe sinus bradycardia, asystolic cardiac arrest and atrioventricular block, and tachyarrhythmias (1-14).

Respiratory complications also may occur secondary to spinal cord injury (5,15).

Moreover, head injuries also may result in cardiovascular, respiratory, metabolic-electrolytic and other complications (10-14). Serious head trauma may be associated with electrocardiographic abnormalities and with rhythm disturbances. Initially, sympathetically mediated cardiovascular responses may ensue, with neurogenic hypertension-elevations in blood pressure and elevations in heart rate and cardiac output.

Traumatic diabetes insipidus (DI) has been observed after severe and after minor closed head trauma (13,16-23).

We wish to report a young male who, after a fall suffered high cervical spinal cord and head injuries. These injuries led to spinal shock, marked sinus bradycardia and asystolic cardiac and respiratory arrest, recalcitrant central traumatic DI, and death within approximately 7 weeks.

CASE HISTORY

This 31-year-old male was admitted to the Neurosurgical Unit of the University Hospital on April 22, 1996, after falling while climbing to the top of a tree to pick/gather panas (bread fruit), and striking his head and neck with the ground. Immediately he was unable to move. There is a past history of epilepsy and excessive alcohol (rum) intake. He denied dizziness or palpitations.

Initial examination revealed multiple lacerations and quadriplegia. Rapidly he developed hypotension of 80/50 mm Hg, a minimum of 60 mm Hg, and bradycardia of 38 bpm, dropping to a heart rate (HR) of 25-30 bpm and a respiratory rate of 20 per minute, with some response to a dopamine (IntropinT) drip IV and atropine. Figures 1, 2. electrocardiograms (ECG) were done later in his hospital course.

A cervical CT showed severely comminuted fractures of C 5-6 bodies and laminae, with significant compression of the dural sac. There was fracture dislo-

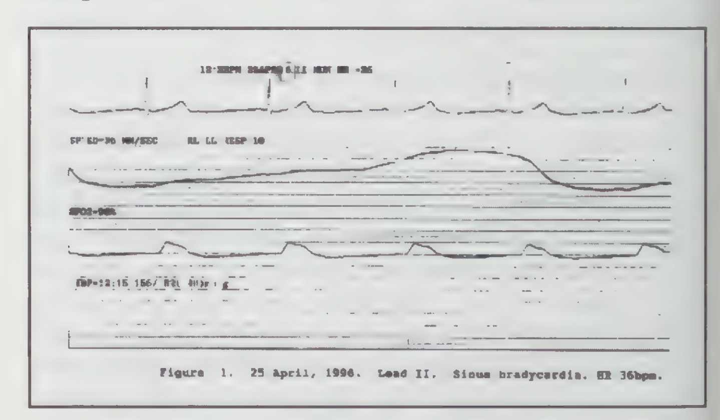


Figure 1. 25 April, 1996. Lead II. Sinus bradycardia. HR 36bpm.

Address: *Charles D. Johnson, M.D.; U.P.R. Medical Sciences Campus, Section of Cardiology; G.P.O. Box 5067, San Juan, Puerto Rico 00936*

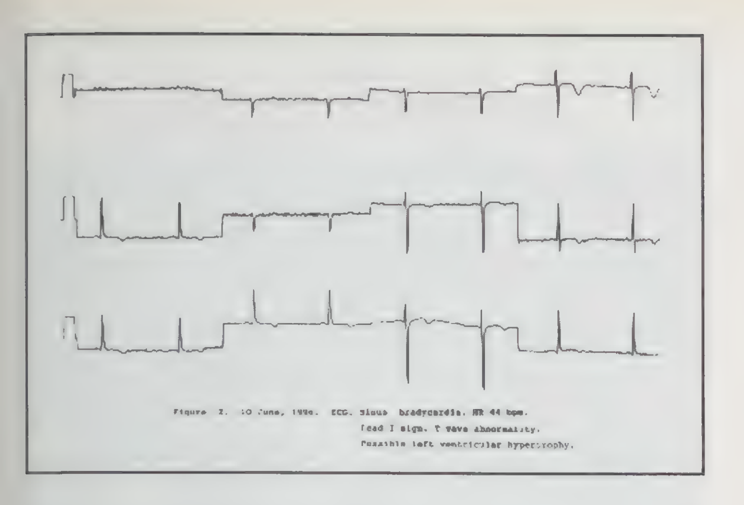


Figure 2. 10 June, 199[illegible]. ECG. Sinus bradycardia. HR 44 bpm.
Lead I sign. T wave abnormality.
Possible left ventricular hypertrophy.

cation of cervical vertebrae C5 - C6 , with cervical spine instability, for which cervical traction was applied.

Subsequently he was observed to have polyuria and polydipsia, with daily intake/outputs of 10 liters. Heart rates rose to 30 - 35 bpm, and later to ~50 bpm, and the hypotension resolved. The Cardiology Service was consulted.

Laboratory data showed marked hypernatremia (serum sodium Na 157 meq/L), a serum chloride 150 meq/L, elevated serum osmolality, decreased urine Sp. gr. (1.005), calcium 6.5 mg/dl and serum phosphorus 6.0 mg/dl and normal glucose.

These were treated with Vasopressin (Pitressin) and later desmopressin acetate (DDAVP[T]), and augmented water intake, by the Endocrinology Service. An external cardiac pacemaker and atropine were kept at the patient's bedside.

May:

5/9: serum osmolality 313 and urine osmolality 227 mosm/kg/H2O .

5/14: the patient underwent anterior copectomy (cadaver graft) and cervical fusion of C5-C6 vertebrae, with good postoperative recovery. A Philadelphia collar was utilized.

During the month, the patients Hr's rose gradually to a range of 45-75 bpm. Symptomatic bradycardia with an episode of cardiac arrest responded to atropine.

The DI was gradually controlled, except some polyuria persisted. Subsequently, the serum sodium normalized, and then it became low, 127-133 meq/L. Pitressin was stopped. The diagnosis of water intoxication was considered. Later in the month, the hypernatremia (148, 162 meq/L) recurred intermittently, with periods of hyponatremia (125, 108 meq/L), and serum osmolality 264 mosm/kg; PO2 78 mm Hg, Oxygen saturation 96%; hemoglobin 7.7 g/dl, hematocrit 22%, plasma/serum cortisol 20 ug/dl (normal 8 am. 5-20 ug/dl).

June: Respiratory arrests with bronchospasm and severe bradycardia ensued, requiring intubation, tracheostomy and mechanical ventilation. The episodes, described as respiratory and cardiac arrests, began with breathing difficulty and were accompanied by cyanosis (but 02 satn were normal- 97, 99 %), convulsions and unconsciousness. The overall HR's were 40-60 bpm.

6/3: Na 148 meq/L.

6/4: Cardiac arrest occurred, with a flat line on the bedside ECG monitor. The patient recovered with CPR.

Laboratory:
glucose 110 mg/dl, Hct 43%, Na 184 meq/L, K 3.5 meq/L, chloride 150 meq/L, CO~ 26 meq/L, calcium 9.9, 8.9 mg/dl, PO 4.6 mg/dl, Mg 2.2 mg/dl, serum osmolality 254, 353 mosm/kg, urine osmolality 116 mosm/kg/H2O.

6/5: HR 56-60 bpm, serum Na 180 meq/L. Pitressin administered. Later, two cardiac arrests occurred. A transvenous pacemaker was placed in the right ventricle, and programmed to a rate of 40-50 ppm, demand mode, less than the patients intrinsic HR of 70 ppm.

6/6: HR's 60 and 78 bpm, Na 162 and 184 meq/L; condition stable. But, on the following day, he was hypotensive, 99/66 mm Hg. The cardiac condition deteriorated further with multiple episodes of arrest, severe bradycardia 23 bpm, pulselessness and unobtainable blood pressure, responding to CPR, atropine and dopamine.

6/8: The patient suffered a respiratory arrest. The Cardiology Service found the intrinsic HR to be 70 bpm, and the pacemaker was capturing well: Vp; threshold 0.5 mA; left at 5 mA.

6/10: at 7:40 am, the patient suffered arresto, with cyanosis, and no pulse, no blood pressure and no spontaneous respirations. Basic and advanced CPR were performed without response. An ECG monitor strip showed mechanical pulsations, and what was interpreted as pacemaker spikes (without visible capture). The programmed low rate of the pacemaker was 60 ppm; however, the alleged pacemaker stimuli/spikes were occurring at a rate slower than 60 ppm and were not regular. The pacemaker was turned off, with only a straight line on the ECG trace-death.

Autopsy, not done.
Pathologic diagnoses: Tracheostomy. Sepsis. Complications of cervical trauma.

DISCUSSION

It is estimated that the annual incidence of spinal cord injury is between 30 and 40 cases per million population. It affects primarily young adults, and 82% of cases are males. Since 1991, 35.9% of cases reported have involved motor vehicle accidents. The next most common causes are gunshot wounds, followed by falls, and then recreational sporting activities. Fifty-three per cent of spinal cord injuries involve cervical spine lesions.

It has been recognized for many years that acute spinal cord injury, especially high cervical cord injury, may be complicated by cardiovascular abnormalities. These abnormalities consist of acute hypotension, spinal shock, and acute cardiac bradyarrhythmias. A diagnosis of Spinal Shock should be entertained in a patient with hypotension and bradycardia (without reflex tachycardia), in the absence of beta-blocker medication usage.

Electrocardiographic abnormalities observed are listed in Table I.

Table I
Electrocardiographic Abnormalities Secondary To Cervical Spinal Cord Injury

1. Bradycardias may be marked and persistent.
   Sinus bradycardia .
   Sinus pauses, sinus arrest.
   Cardiac arrest, Asystole.
   Bradycardia progressing to Cardiac arrest .
   Atrioventricular block, of various degrees .
2. Supraventricular tachyarrhythmias-atrial fibrillation, APCs.
3. Ventricular arrhythmias, including ventricular tachycardia and fibrillation.
4. Repolarization changes. QTC interval prolongation.

References 1-2,4-7

These changes usually are temporary and self-limited, and resolve within 2-3 weeks, but persistent bradycardias have been reported, and extreme bradycardia, asystole and syncope may be delayed for 5 to 9 weeks, and even months afterwards (5-7).

Pathogenesis

The pathogenesis of the hypotension and brady-arrhythmias is related to one or more of the following factors (1-3,5,7,24-28):

- Autonomic dysfunction, instability and imbalance in the autonomic nervous system.
- Severe hypotension often follows cervical cord injury because the lesion interrupts the descending sympathetic pathways.
- Bradycardia characteristically accompanies the low blood pressure.
- Disruption of cardiac sympathetic pathways located in the cervical cord, with acute sympathetic withdrawal and resultant dominant, unopposed parasympathetic activity and vagal reflexes and tone stimulation on the heart.
- Elimination or diminution in sympathetic arteriolar tone-vasodilation.
- Acute transection or compression of the spinal cord.
- Thus, neurogenic hypotension or spinal shock shows an absence of the tachycardia which characteristically occurs with hypovolemic shock.
- Blood loss, hypoxia, brainstem injury and ischemia. Associated myocardial injury.
- Inability to breathe spontaneously. Absent pulmonary inflation and pulmonary stretch receptors-vagal reflexes. Pulmonary embolization.
- Bradycardia is often associated with tracheal suction, changes in the body position and turning the patient to the prone position, belching, bladder triggers, distention of abdominal viscera, defecation and external triggers-stimulation of airway receptors.
- Severe bradycardia and even asystole with sudden death may result from tracheal suction.

- Cardiac arrest may result from respiratory failure, in the presence of lesions above the T1 level, through unopposed vagal stimulation induced by laryngeal suction or intubation, or by sudden hyperkalemia from administration of suxamethonium as a muscle relaxant.

Respiratory complications also are common after cervical spinal cord injury. These complications comprise respiratory insufficiency, pneumonia, atelectasis, diaphragmatic dysfunction, and after high cervical cord injury respiratory embarrassment is the rule. Damage to cervical or to high thoracic spinal levels creates the risk of ventilatory failure due to paralysis of intercostal, abdominal muscles, the diaphragm, or both. Indeed, these patients may succumb to respiratory failure and respiratory infections (5,9,15,28,31).

Head Injuries

Head injuries are also commonly seen by doctors in hospitals. Two to three thousand cases per million population are admitted to hospitals each year, and three to four times this number of patients are seen in other medical facilities, such as Emergency Rooms and trauma centers, etc.

Head injuries too may result in cardiac complications and electrocardiographic abnormalities. Sympathetically-mediated elevations in blood pressure, heart rate and cardiac output may follow. This autonomic dysfunction systolic hypertension, neurogenic hypertension, may lead to myocardial ischemia and cardiac dysrhythmias. Also, vagal tone may be augmented.

Head trauma-induced electrocardiographic abnormalities (prolonged QT interval, prominent T waves, inverted T waves, ST segment deviations, and U waves) and rhythm disturbances (sinus bradycardia-increased vagal tone-atrial and ventricular ectopy-increased sympathetic tone-heart block and intraventricular conduction disturbances) may result (10-12,14).

Posttraumatic central, neurogenic DI (CDI) is a recognized result of severe and minor head trauma. Previous large series of cases reported an incidence of less than 1%; however, now, head trauma is a frequent cause of DI. Posttraumatic DI is increasing in frequency, and blunt or penetrating cranial trauma represents approximately 18% of all causes of DI. This is related to the increased numbers of head injuries due to automobile accidents, and the longer survival of patients after extensive injuries as a result of modern medicine.

Posttraumatic DI is more likely to be associated with severe degrees of closed head trauma involving loss of consciousness, skull fracture and more generalized neurological deficits. It usually presents within 12 to 24 hours after the initial insult, but may be delayed up to several months or even years post-trauma. Posttraumatic DI is frequently transient.

Central neurogenic DI is caused by damage to the hypothalamus or pituitary stalk. Traumatic injury to the neurohypophyseal nuclei and posterior pituitary tracts affect the synthesis and release of vasopressin-anti-diuretic hormone (ADH).

Clinical pathogenetic patterns of traumatic CDI are:

Acute:

1. Transient. Partial or complete resolution often occurs, the most common pattern, comprising 50-60% of cases; resolves within several days (3-5) or rarely several weeks.

2. Permanent or prolonged DI; 30-40% of cases. Rarely a late recovery occurs.

3. A triphasic response; the least frequent, 5-10%.
   a. Initial phase; polyuria for a few days.

   b. Antidiuresis, for 2-14 days; potentially leading to water retention and hyponatremia; attributed to the release of vasopressin stored in granules/ axonal necrosis of neurons.

   c. Recurrent, Permanent/chronic DI; from axonal necrosis and cessation of vasopressin production.

Chronic:

Recognition of the triphasic response can help to prevent inappropriate therapy leading to hyponatremia during the second phase, as probably occurred in our patient (9,12-13,16-23).

The differential diagnosis of DI includes:

Table II
Differential Diagnosis of Diabetes Insipidus

1. Primary polydipsia. Psychogenic. CNS sarcoidosis.
2. Osmotic diuresis. Polyuria: Cushing's, Parkinson's, glucocorticoids, lithium.
3. Fluid overload.
4. Nephrogenic Diabetes Insipidus — congenital/familial; acquired.
5. The polydipsia-polyuria syndromes.

References 9, 12-13, 16-23.

Posttraumatic CDI may be diagnosed on the basis of the following criteria:

Table III
Diagnostic Criteria of Diabetes Insipidus

1. Polydipsia > 120 ml/kg/d or > 3.5 L/d.
2. Polyuria > 30-90 ml/kg/d or >2.5-5 to >20 L/d of urine.
3. Urine - dilute, colorless, hypotonic, low osmolality, low Sp. gr. 1.000-1.010 (normal >1.015), osmolality 50-300 mosm/kg/H20 (normal 100-900 mosm/kg/H2O).
4. Serum/Plasma osmolality increased, 310-320 mosm/kg (nor 275-295 mosm kg/H2O). Hypernatremia, sodium > 140-145 meq/L.
(hyponatremia is the most common electrolyte abnormality following head trauma).
5. Hypertonic dehydration. Volume deficit may occur if the capacity to drink or access to water is impaired (patient unconscious, neurologic deficit, physical restraint, endotracheal intubation)-may result in neurological symptoms and a diminished level of consciousness.
6. Plasma ADH < 1.1 ng/L (normal 1.3- 4.1 ng/L).
7. Cardiovascular-diminished stroke volume, heart rate, hypoperfusion, orthostatic hypotension, weak arterial pulses, cold clammy skin, rapid shallow respirations.
8. Possible Anterior pituitary dysfunction.
9. Water Deprivation Test/ Dehydration Test- urine Sp gr. < 1.010; 50-500 mosm/kg., serum 295-320 mosm/kg.
10. Vasopressin Challenge Test / Desmopressin acetate-0.05-0.1 ml IN or 1 ug SC or IV. Decreases thirst and the urine output. Urine osmolality increases 9% to over 100% (normal no change or < 5% change).

References 9,13,16-23

Management of these complications of spinal cord injury are addressed in Table IV:

Table IV A
Management of Spinal Cord Injury Patients

1. Hospital. A speciality ward. Trauma care.
2. Spinal resuscitation.
3. Immobilization-immobilize the neck and spine gently at the injury site. Maintain the head in a neutral position.
4. Assessment-Maintain ventilation. Protect against shock.
5. Investigation Testing: x-rays, CT, CT myelogram, MRI.
6. Cord compression-usually open surgical decompressive laminectomy and fusion.

Continúa

7. Corticosteroids, immediately in high dosage; methylprednisolone 30 mg/kg loading dose by IV bolus, followed by 5.4 mg/kg/hr for 23 hours.
8. Experimental : GM-1 ganglioside for 3-4 weeks. Free radical scavengers. N-methyl-D-aspartate (NMDA) antagonists.
9. Anatomic realignment of the spinal cord by skeletal traction, skull fixation, etc.
10. Rehabilitation Medical management
Subsequent care of residual neurologic deficits (paraplegia, quadriplegia); treatment of spacticy. Care of skin, bladder and bowels. physical and occupational therapy; passive mobilization and positioning. Nutrition. Psychosocial.
11. Prevention of thromboemboli-graded support stockings, anticoagulants.
12. Adenohypophyseal hormones, possibly.

Table IV B

1. Hypotension:
   a. hemodynamic monitoring; Swan-Ganz catheter fluid replacement.
   b. Cardiac support; inotropic, chronotropic, vasoconstriction.
   Maintain a mean arterial pressure over 80 mm Hg-continuous IV infusion dopamine 5-15 ug/kg/min. phenylephrine,
   Maintain cardiac output: dobutamine 5-15 ug/kg/min.
   Elevate the legs to improve venous return.
2. Bradyarrhythmias:
   a. vagolytic (cholinergic blockade) drug therapy: atropine bolus injection IV, IM.
   b. ephedrine
   c. isoproterenol infusions
   d. propantheline bromide (Pro-Banthine^{T})
   e. Cardiac Pacing-external, Zoll, transvenous, short or long term/ permanent.
   f. Motion bed
3. Pulmonary-improve ventilation: oxygenation, IPPB. If VC < 500 ml: endotracheal intubation, following administration of atropine to prevent reflex cardiac arrest.
4. Prevention:
   a. prevent hypoxia-avoid tracheal stimulation, suctioning, etc, or administer oxygen, increase ventilation, atropine pre/prior to tracheal suctioning and prior to turning the patient to the prone position.
   b. if a muscle relaxant is needed, use a non-depolarizing drug (not suxamethonium).

References 2,5-6,9,15-16,22-23,25,28-30

Table IV C
Management of Central Diabetes Insipidus

1. Monitor serum and urine electrolytes, fluid intake and output.
2. Arginine vasopressin (Pitressin), acqueous vasopressin 5-10 units/d subc, IM (never IV).
3. Lypressin (Diapid[T])-Nasal sprays : 4-12 sprays in each nostril/d.
4. Desmopressin acetate (DDAVP[T]): 10-40 ug (0.1-0.4 ml)/ d. Nasal spray (intranasal). Injection 2-4 ug/d IV, subc, IM. Tablet, oral 0.1- 0.8 mg/d. Adverse reaction hyponatremia.
5. Hypernatremia-fluids, volume: oral, IV D5 W. (avoid overaggressive fluid administration); reduce aggravating factors (glucocorticoids).
6. Chlorpropamide (Diabinese[T]) 100-500 mg /d. Danger: hypoglycemia.
7. Hydrochlorothiazide (HydroDiuril[T]) 50-100 mg/d.
8. Carbamazepine (Tegretol[T]) 200-600 mg/d.
9. Clofibrate (Atromid-S[T]) 500 mg q. 6 hr.
10. Chronic Central Diabetes Insipidus DDAVP[T] (desmopressin).

References 9,13,16-23

Temporary transvenous cardiac pacing proved useful in the management of this patient.

In our patient, it is difficult to indite the specific and primary mode of demise. It is doubtful that the tracheal suctioning performed 20 minutes prior was the trigger for his arrest. Whether primary respiratory or primary cardiac arrest initiated the patients death could not be determined.

1. Atromid-S-clofibrate. Wyeth-Ayerst Labs., Philadelphia, PA. USA.
2. DDAVP-desmopressin acetate. Rhone-Poulenc Rorer Pharmaceuticals. Collegeville, PA.
3. Diabinese-chlorpropamide. Pfizer Labs Division. New York, NY.
4. Diapid-lypressin. Sandoz Pharmaceuticals Corp. East Hanover, NJ.
5. Dobutrex-dobutamine hydrochloride. Eli Lilly, Indianapolis, IN.
6. HydroDiuril-hydrochlorothiazide . Merck & Co., West Point, PA.
7. Intropin-dopamine hydrochloride. DuPont Pharmaceuticals, Wilmington, DE.
8. Pro-Banthine-propantheline bromide. Roberts Pharmaceutical Corp. Eatontown, NJ.
9. Solu-Medrol-methylprednisolone sodium succinate. Upjohn Co. Kalamazoo MI.
10. Tegretol-carbamazepine-Basel Pharm (Ciba Geneva Pharm). Summit,NJ

Acknowledgements: Dr. Nathan Rifkinson, MD Chief of the Department of Neurosurgery, University Hospital, and the Endocrinology Service, Chief Dr. Francisco Aguilo, MD, University Hospital.

Resumen: *Reportamos a un paciente masculino, quien después de una caida sufrió lesiones a la espina cervical y a la cabeza. Estas lesiones causaron estado de choque espinal, bradicardia severa y arrestos cardiorespiratorio asistólico. Este paciente que padeció de diabetes insipidus central también, murió en aproximadamente siete semanas.*

REFERENCES

1. Kantor HL, Krishnan SC. Cardiac problems in patients with neurologic disease. Ed. MH Crawford. Cardiology Clinics 1995, No. 2, 13: 179-208
2. Lehmann KG, Lane JG, Piepmeier JM, Batsford NP. Cardiovascular abnormalities accompanying acute spinal cord injury in humans: incidence, time course and severity. JACC 1987; 10: 46-52
3. Atkinson PP, Atkinson JLD. Spinal shock. Mayo Clinic Proc. 1996; 71: 384-9
4. Piepmeier JN, Kenneth LB, John LG. Cardiovascular instability following acute cervical spinal cord trauma. Central Nervous System Trauma 1985; 2: 153-60
5. Winslow EBJ, Lesch M, Talano JV, Meyer PR. Spinal cord injuries associated with cardiopulmonary complications. SPINE 1986; 11: 809-12
6. Silbert PL, Davis MJE. Late asystole in high cervical spinal cord injury: case report. Paraplegia 1990; 28: 137-140
7. Dixit S. Bradycardia associated with high cervical spinal cord injury. Surgical Neurology 1995; 43:514

8. Walker MD. Acute spinal cord injury. Edit. N Engl J Med 1991; 324: 1885-87

9. Marshall LF. Spinal cord injury. Chap. 438, in Cecil Textbook of Medicine. (Ed J.C. Bennett, F. Plum). 20th Edition. Philadelphia, W.B. Saunders Co. 1996, pp 2139-2140

10. Miller JD. Head injury. J of Neurology, Neurosurgery, and Psychiatry 1993; 56: 440-47

11. Wirth R, Fenster PE, Marcus FI. Transient heart block associated with head trauma. J of Trauma 1988; 28: 262-64

12. Kaufman HH, Timberlake G, Voelker J, Pait TG. Medical complications of head injury. In, Medical Clin N. Amer. 1993; 77: No 1, 43-60

13. Adam P. Evaluation and management of diabetes insipidus. AFP 1997; 55: 2146-2160

14. Hersch C. Electrocardiographic changes in head injuries. Circulation 1961; 23: 853-60

15. Lemons VR, Wagner FC. Respiratory complications after cervical spinal cord injury. SPINE 1994; 19: 2315-2320

16. Verbalis JG, Robinson AG, Moses AM. Postoperative and post-traumatic diabetes insipidus. Frontiers of Hormone Research. 1985; 13: 247-265 (S. Karger, Basel)

17. Notman DD, Mortek MA, Moses AM. Permanent diabetes insipidus following head trauma: observation of ten patients and an approach to diagnosis. J Trauma 1980; 20: 599-602

18. Blevins LS, Wand GS. Diabetes insipidus. Critical Care Medicine 1992; 20: 69-79

19. Kern KB, Meislin HN. Diabetes insipidus: Occurrence after minor head trauma. J Trauma 1984; 24: 69-72

20. Golonka JE, Richardson JA. Postconcussive hyperosmolality and deficient thirst. Am J Medicine 1970; 48: 261-67

21. Oh MS, Carroll HJ. Disorders of sodium metabolism: hypernatremia and hyponatremia. Critical Care Medicine 1992; 20: 94-103

22. Bianco CM. Diabetes insipidus. Your role in managing this multifaceted disease. Am J. Nursing 1996; 96: 30-31

23. Singer I, Oster JR, Fishman LM. The management of diabetes insipidus in adults. Arch Intern Med 1997; 157: 1293-1301

24. Greenhoot JH, Mauck H. The effect of cervical cord injury on rhythm and conduction. Am Heart J. 1972; 83: 659-62

25. Frankel HL, Mathias CJ, Spalding JMK. Mechanisms of reflex cardiac arrest in tetraplegic patients. Lancet 1975; 1183-85, Dec- 13

26. Evans DE, Kobrine AI, Rizzohi H. Cardiac arrhythmias accompanying acute compression of the spinal cord. J Neurosurgery 1980: 52: 52-9

27. Zipnick RI, Scalea TM, Trooskin SZ, et al. Hemodynamic responses to penetrating spinal cord injuries. J Trauma 1993; 35: 578-583

28. Mathias CJ. Bradycardia and cardiac arrest during tracheal suction- mechanisms in tetraplegic patients. European J Intensive Care Medicine 1976; 2: 147-156

29. Abd AG, Braun NMT. Management of life-threatening bradycardia in spinal cord injury. Chest 1989; 95: 701-702

30. Gilgoff IS, Ward SLD, Hohn AR. Cardiac pacemaker in high spinal cord injury. Arch Phys Med Rehabil 1991; 72: 601-603

31. Wagner R, Jagoda A. Spinal cord syndromes. Emergency Medicine Clinics of N. America. 1997; 15: No. 3, pp 699-711

Journal Watch:

Robert A Burt JD
The Supreme Court Speaks:

Not Assisted Suicide but a Constitutional Right to Palliative Care

N Eng J Med 1997; 337:1234-6

La Corte Suprema de los Estados Unidos rechazó el concepto de un derecho constitucional al suicidio médico- asistido (1,2).Pero a su vez le requirió a todos los estados de la unión que se aseguraran que ninguna de sus leyes obstruye el ofrecer tratamiento paliativo efectivo, particularmente para aliviar el dolor y otros síntomas, en pacientes con una perspectiva de pocos meses de vida. La distinción establecida entre la aceptación "pasiva" de los acontecimientos y la asistencia "activa" en el proceso de morir tendrá un efecto beneficioso en la práctica médica.

El pronunciamiento de la Corte Suprema que no es suicidio- asistido la sedación necesaria para controlar síntomas en la fase terminal de la vida permite un tratamiento paliativo más agresivo. Las leyes y política pública en muchos estados que limitan el uso de opiáceos son buenos candidatos para ser invalidadas haciendo uso del criterio establecido por la Corte. Armados con el derecho constitucional de pacientes para un tratamiento paliativo efectivo, los médicos pueden mejor proteger su amenazada prerrogativa profesional de recetar dosis altas de sedantes y de opiáceos a pacientes terminales.

José Ramírez Rivera MD
Caparra Heights
700 Eucalipto
San Juan, Puerto Rico 00920

References:

1. Washibgton v. Glucksberg, 117 S. Ct. 2258 (1997)
2. Vacco v. Quill, 117 S. Ct. 2293 1997)

Vol. 90 • 4 - 5 - 6 / 1998 • Pág. 103

Correspondencia Recibida:

La Oración del Anestesiólogo y la Práctica de Anestesiología

Miguel Colón Morales, M.D., Director
Depto. de Anestesiología
Hospital del Maestro

¿Es la anestesia peligrosa? Sin duda alguna lo es, como cualquier anestesiólogo conciente y responsable estará dispuesto a confirmar.

Sin embargo, apesar de todos nuestros esfuerzos, apesar de todos nuestros conocimientos y destrezas y apesar de todo el monitoreo, desgracias a veces ocurren a nuestros pacientes. Algunas de ellas pueden ser clasificadas como "prevenibles " y el anestesiólogo conciente y responsable enfrenta muy pocas de ellas. Otras pueden clasificarse como "imprevisibles" y debido a la respuesta de los pacientes y a su condición médica.

Debido a ese eterno peligro del estado de anestesia; debido al riesgo que todo paciente tiene que asumir cuando recibe anestesia para cualquier procedimiento; debido a que los médicos no somos DIOS, pero solamente su instrumento para servir y ayudar otros seres humanos y por muchas otras razones, existe una necesidad para que la Oración del Anestesiólogo por I.G. Converse, M.D. sea expuesta en la oficina de todo anestesiólogo y en toda Sala de Operaciones.

Muchos pacientes y algunos médicos no están completamente concientes de los peligros de la anestesia y de la responsabilidad que el anestesiólogo debe asumir y de los conocimientos y destrezas que debe poseer y ejecutar para protejer la vida de su paciente. El trabajo del anestesiólogo es frecuentemente menospreciado hasta que ocurre una desgracia y/o ocurre la muerte. Concientización del público sobre la necesidad de que la práctica de anestesia debe ser considerada la práctica de medicina por médicos especialistas responsables, es absolutamente necesario si vamos a evitar muertes y complicaciones innecesarias en aquellos pacientes que necesiten y reciban anestesia.

¿Qué mejor forma para crear esa conciencia sobre los peligros reales de la anestesia, qué aceptando con humildad y valor que los médicos y en particular, nosotros los anestesiólogos, somos seres humanos preparados para servir a nuestros pacientes con lo mejor de nuestras habilidades y por la Gracia de Nuestro Señor... ?

La "Oración del Anestesiólogo" debe estar expuesta en toda oficina de anestesiólogos y en toda Sala de Operaciones. También debe estar presente en la mente del anestesiólogo cuando esté practicando su especialidad. Ambas, su confiznza y au imagen, serán mejoradas.

Amén.

ORACION DEL ANESTESIOLOGO

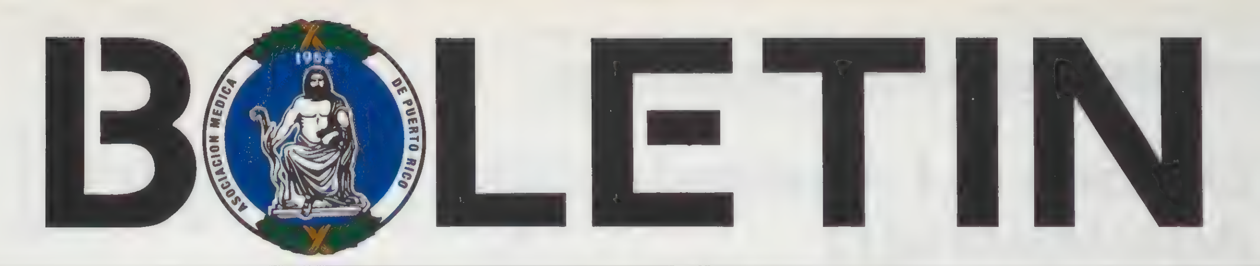
Bendice estas manos y esta mente,
Señor mío, para que puedan cuidar
con seguridad a los que sean confiados
a ellas en el día de hoy.

¡Permite que mis manos se mantengan
ágiles, mi mente alerta y mi visión
clara para que no le ourra a mis
pacientes desgracia anestésica alguna!

Auque ellos están en mis manos,
mis manos están en las tuyas, Señor mío,
por favor, guíalas bien.

Amén.

I.G. Converse, M.D.



Instrucciones para los Autores*

El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que pudiera ser de interés general para la profesión médica.

Se urge a los autores se esfuercen en perseguir claridad, brevedad, e ir a lo pertinente en sus manuscritos, no importa el tema o formato del manuscrito.

El artículo, si se aceptara, será con la condición de que se publicara únicamente en la revista.

Para facilitar la labor de revisión de la Junta Editora y la del impresor, se requiere de los autores que sigan las siguientes instrucciones:

Manuscrito

El manuscrito completo, incluyendo las leyendas y referencias deberán estar escritos en maquinilla a doble espacio; por un sólo lado de cada página, en TRIPLICADO y con amplio margen. En página separada deberá incluirse lo siguiente: título, nombre de autor(es) y su grado (ej.: MD, FACP), ciudad donde se hizo el trabajo, el hospital o institución académica, patrocinadores del estudio, y si un artículo ha sido leído en alguna reunión o congreso, así debe hacerse constar como una nota al calce.

El manuscrito debe comenzar con una breve introducción en la cual se especifique el propósito del mismo. Las secciones principales (como por ejemplo: materiales y métodos) deben identificarse con un encabezamiento en letras mayúsculas.

Artículos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos: introducción, Materiales y Métodos, Resultados, Discusión, Resumen (en español e inglés), Reconocimiento y Referencias.

Artículos referentes a estudios de casos aislados deben organizarse en la siguiente forma: Introducción, Materiales y Métodos si es aplicable, Observaciones del Caso, Discusión, Resumen (en español e inglés), Reconocimientos y Referencias.

Nomenclatura

Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea se usará con preferencia el sistema métrico de pesos y medidas.

Tablas

Las tablas deben aparecer en hojas separadas. Estas deben incluir el título, y el número de la tabla debe estar en romano. Los símbolos de unidades deben limitarse al encabezamiento de las columnas. Se deben omitir líneas verticales en la tabla. Se usará en las tablas el mismo idioma en el cual está escrito el artículo. Deben limitarse las tablas a solo aquellas que contribuyan al mejor entendimiento del manuscrito.

Ilustraciones

Las fotografías y microfotografías se someterán como copias en papel de lustre, sin montar o en transparencias. En el reverso de la figura debe aparecer el número de la figura (arábigo) y el autor. Debe indicarse la parte superior de la ilustración.

Resumen

Un abstracto no mayor de 150 palabras debe acompañar los manuscritos. Debe incluir los puntos principales que ilustren la substancia del artículo y la exposición del problema, métodos, resultados y conclusiones.

Referencias

Las referencias deben ir numeradas sucesivamente de acuerdo a su aparición en el texto. Los números deben aparecer en paréntesis al nivel de la línea u oración. Al final de cada artículo las referencias deben aparecer en el orden numérico en que se citan en el texto. Deben utilizarse solamente las abreviaturas para títulos de revistas científicas según indicadas en el "Cumulative Index Medicus" que publica la Asociación Médica Americana. Las referencias deben seguir el patrón que se describe a continuación.

1. Para artículos de revistas: Apellido(s) e iniciales del nombre del autor(es), título del artículo, nombre de la revista, año, volumen, páginas. Por ejemplo:
   Villavicencio R: Soplos inocentes en pediatría, Bol Asoc Méd P Rico 1981; 73: 479-87. Si hay más de 7 autores, incluir los primeros 3 y añadir et al.
2. Para citación de libros donde el autor(es) del capítulo citado es a su vez el (los) editor(es): Apellido(s) e iniciales del autor(es), título del libro, número de edición, ciudad, casa editora, año y página. Por ejemplo:
   Keith JD, Rowe RD, Vlad P: Heart disease in infancy and childhood, 3d. Ed., New York, MacMillan, 1978: 789
3. Para citación de libros donde el editor(es) no es el autor(es) del capítulo citado se añade el autor(es) del capítulo y el título del mismo. Por ejemplo:
   Olley PM: Cardiac arrythmias; In: Keith ID, Rowe RD, Vlad P Eds. Heart disease in infancy and childhood, 3d Ed., New York, MacMillan, 1978: 275-301

Cartas al Editor

Se publicarán a discreción de la Junta Editora. Deben estar escritas en maquinilla a doble espacio, no deben ser mayores de 500 palabras, ni incluir más de cinco referencias.

ARTICULO DEBERA SER ACOMPAÑADO POR UN "DISKETTE".

**Estas "Instrucciones para los Autores" son de acuerdo a las normas establecidas por el Comité Internacional de Editores de Revistas Médicas en sus "Requisitos Uniformes para Manuscritos Sometidos a Revistas Bio-Médicas".*

Instructions to Authors*

The Bulletin will accept for publication contributions relating to the various areas of medicine, surgery and allied medical sciences. Special articles and correspondence on subjects of general interest to physicians will also be accepted. All material is accepted with the understandig that is to be published solely in this journal.

All authors are urged to seek clarity, brevity, and pertinence in the manuscripts regardless of subject or format.

In order to facilitate review of the article by the Editorial Board and the work of the printer, the authors must conform with the following instructions:

Manuscripts

The entire manuscript, including legends and references should be typewritten double spaced in TRIPLICATE with ample margins. A separate title page should include the following: title, authors and their degrees (e.g. MD, FACP), city where the work was done, hospital or academic institutions, acknowledgement of financial sponsors, and if the paper has been at a rneeting the place and date should be given.

The manuscripts should start with a brief introductory paragraph or paragraphs which should state its purpose. The main sections (for example, Materials and Methods) should be identified by heading in capitai letters.

Articles reporting the results of clinical studies or laboratory investigation should be organized under the following headings: Introduction, Materials and Methods, Result if indicated, Discussion, Summary in English and Spanish, Acknowledgments if any, and References.

Nomenclature

Generic names ofdrugs should be used; trade names my also be given in parenthesis, if desired, metric units of measurement should be used preferentially.

Tables

These should be typed on separate sheets with the title and table number (Roman) centered. Symbol for units should be confined to the column headings. Vertical lines should be omitted. The language used in the tables must be the same as that of the article. Include only those tables which will enhance the understanding of the article. They should supplement, not duplicate the text.

Figures

Photographs and photomicrographs shoul be submitted as glossy prints (unmounted) or slides. They should be labeled in the back with the name of the authors and figure number (Arabic) and the top should be indicated. Legend to the figures should be typed on a separate sheet.

Summary

An abstract not longer than 150 words should accompany all articles. It must include the main points that present the core of the article and the exposition of the problem, method, results, and conclusions.

References

These should be numbered serially as they appear in the text. The number should be enclosed in parenthesis on the line or writing and not as superscript numbers. At the end of the article references should be listed in the numerical order in which they are first cited in the text. The titles of journals should obe abbreviated according to the style used in the "Cumulative Index Medicus" published by the American Medical Association. The correct forms of references are as given below:

1. For periodicals: Surname and initials of author(s), title of article, name of journal, year, volume, pages. For example:
   Villavicencio R.: Soplos inocentes en pediatría. Bol Asoc Med P Rico 1981; 73: 479-87. If there are more than 7 authors list only 3 and add et al.

2. For books when the authors of the cited chapter is at the same time the editor: Surname and initials of author(s), title, edition, city, publishing house, year and page. For example:
   Keith JD, Rowe RD, Vlad P: Heart disease in infancy and childhood, 3d Ed., New York, MacMillan, 1978: 789

3. For chapter in book when the author of the chapter is not one of the editors:
   Olley PM: Cardiac arrythmias: In: Keith JD, Rowe RD, Vlad P. Eds. Heart disease in infancy and childhood, 3d Ed. New York, MacMillan, 1978, 275-301

Letters to the Editor

Will be published at the discretion of the Editorial Board. They should be typewritten double-spaced, should not exceed 500 words nor more than five references.

ARTICLES SHOULD BE ACCOMPANIED WITH A "DISKETTE".

**The above "Instructions to Authors" are according to the format required by the International Committee of Medical Journal Editors in its "Uniform Requierements for Manuscripts Submitted to Biomedical Journals".*

El Ácido Fólico y la Prevención de Defectos del Tubo Neural (NTD)

El ácido fólico, vitamina del complejo B, está relacionado con el metabolismo de aminoácidos y la síntesis de RNA y DNA. De no estar presente en cantidades suficientes al momento del cierre del tubo neural en el embrión (día 26-28 del período de gestación) se afecta la formación de tejido, provocando diferentes defectos. Algunos de estos defectos son la condición de Anencefalia (ausencia de cerebro), y Meningocele o Espina Bífida. Los bebés que nacen con estos defectos van a presentar afección simultánea de los sistemas nervioso central, musculoesqueletal, génitourinario y problemas de aprendizaje asociados. A tales efectos van a necesitar de servicios de salud especializados y sub-especializados. Esto representa una carga emocional, social y económica para los padres.

En Puerto Rico, anualmente 1.6 casos se estiman por cada mil nacimientos vivos, lo que equivale al de la incidencia en Estados Unidos.

Estudios realizados por diferentes investigadores han comprobado que la ingesta de 0.4 mg de ácido fólico y consistentemente durante la edad reproductiva, 10-50 años, disminuye hasta en un 50% la ocurrencia de algunos defectos del tubo neural (NTD). También estos estudios han comprobado que la ingesta de 400 mcg de ácido fólico diarios reduce en 70% la recurrencia de NTD en mujeres que han tenido un bebé con uno de estos defectos.

Los cereales Kellogg's Corn Flakes y Kellogg's Product 19 proveen el 45% y 100% respectivamente del ácido fólico que se necesita diariamente.





NATIONAL LIBRARY OF MEDICINE
NLM 01277806 7
Conéctate a
INTERNE
http://www.ssspr.co
RED DE SALUD
Accesa el listado de más de 10,000 médicos, dentistas, laboratorios y hospitales de la red de Triple-S, por localización y especialidad.
SERVICIOS DE SALUD
Consigue información detallada sobre:
▸ productos y servicios de salud de Triple-S
▸ directorio por departamento de la oficina central y teléfonos de las regionales.
REVISTA VITAL
Ponte al día sobre lo último en salud y medicina; haz una conección directa con otras páginas de salud en Internet.
E-MAIL
Solicita información de Triple-S o envía tus comentarios y sugerencias a través del conveniente correo electrónico.
GRUPO CORPORATIVO
Descubre las alternativas que te ofrecen las subsidiarias del Grupo Corporativo Triple-S: seguros de vida, incapacidad, propiedad y contingencia, además de las cuentas IRA y financiamiento de primas.
Sometido para aprobación al Comisionado de Seguros de P.R. en 4/15/98.

Boletín

VOL. 90 NUM. 7 - 8 - 9 - 10 - 11 - 12 JULIO - DICIEMBRE 1998

ASOCIACION MEDICA DE PUERTO RICO 1902

ASOCIACION MEDICA de puerto rico

FOTOGRAFIA POR: DR. ANSELMO MIRANDA MARTIR

ASOCIACION MEDICA DE PUERTO RICO

BOLETIN

VOL. 90 • NUM. 7 - 8 - 9 - 10 - 11 - 12 • JULIO a DICIEMBRE 1998

OFICINAS ADMINISTRATIVAS

Asociación Médica de Puerto Rico
Ave. Fernández Juncos Núm. 1305 • Apartado 9387
San Juan, Puerto Rico 00908 • Tel (787) 721-6969

SUBSCRIPCIONES Y ANUNCIOS

Asociación Médica de Puerto Rico
Apartado 9387 • San Juan, P.R. 00908 • Tel. (787) 721-6969

Publicación trimestral - $40.00 anuales. El Boletín se distribuye a todos los miembros de la Asociación Médica de Puerto Rico como parte de su cuota anual.
Todo anuncio que se publique en el Boletín de la Asociación Médica de Puerto Rico deberá cumplir con las normas establecidas por la Asociación Médica de Puerto Rico y la Asociación Médica Americana.
La Asociación Médica de Puerto Rico no se hace responsable por los productos o servicios anunciados. La publicación de los mismos no necesariamente implica el endoso de la Asociación Médica de Puerto Rico.
Todo anuncio para ser publicado debe reunir las normas establecidas por la publicación. Todo material debe entregarse listo para la imprenta y con sesenta días de anterioridad a su publicación. La AMPR no se hará responsable por material y/o artículos que no cumplan con estos requisitos.
Todo artículo recibido y/o publicado está sujeto a las normas y reglamentos de la Asociación Médica de Puerto Rico. Ningún artículo que haya sido previamente publicado será aceptado para esta publicación. La Asociación Médica de Puerto Rico no se hace responsable por las opiniones expresadas o puntos de vista vertidos por los autores, a menos que esta opinión esté claramente expresada y/o definida dentro del contexto del artículo.

Boletín de la Asociación Médica de Puerto Rico is published quarterly for $40.00 per year by Asociación Médica de Puerto Rico, 1305 Fernández Juncos Ave. P.O. Box 9387, San Juan, Puerto Rico 00908.
"POSTMASTER" Send address changes to Boletín Asociación Médica de Puerto Rico, 1305 Fernández Juncos Ave. P.O. Box 9387, San Juan, Puerto Rico 00908.

Catalogado en Cumulative Index e Index Medicus.
Listed in Cumulative Index and Index Medicus. No. ISSN - 0004-4849

CONTENIDO

ampr
FUNDADO 1903



Un saludo muy cordial a todos nuestros lectores

Este Boletín de este trimestre, se publican las ediciones de Septiembre y Diciembre en un solo ejemplar. Las razones por ésto son multifactoriales, además, los estragos del huracán Georges afectaron el flujo de información a la Junta Editora, incluyendo la comunicación de y hacia los autores, de igual forma los revisores de artículos. Es nuestra intención que en este próximo año 1999 la revista continúe con su proyección de cuatro ediciones al año y podamos empezar a publicar suplementos que resuman algunos de los temas más relevantes en nuestra medicina.

Queremos extender nuestro agradecimiento a todos los revisores de artículos durante el año 1998. Su trabajo desinteresado y diligencia en mantener la agendas de tiempo del Boletín son apreciadas por toda la Junta Editorial y sobre todo la dedicación, que ha hecho posible que esta revista continúe con el grado de excelencia que aspiramos tener.

Muchas Felicidades y un Próspero Año 1999.

Dr. Robert Hunter Mellado
Dr. Pedro M. Mayoral

Mensaje:

La Medicina del Futuro

Por: Gonzalo González Liboy, M.D., FACP
Presidente AMPR

En la actualidad y durante todos los años que nos precedieron, la gran mayoría de nuestro trabajo diagnóstico se ha basado en el diagnosticar enfermedades establecidas. A estas enfermedades le aplicábamos el tratamiento más apropiado con intenciones paliativas o correctivas. Nuestra labor era muy limitada en lo tocante a la prevención. No es hasta el siglo pasado que la clase médica comienza a darle una importancia relevante a la prevención. Surgen así las vacunas. Por añadidura comenzamos los médicos a darnos cuenta de la importancia del diagnóstico temprano sobre todo en los casos de malignidad. Los estudios de exploración en el caso de cáncer nos permiten un diagnóstico temprano y un tratamiento eficaz, cuando aun estas lesiones patológicas, están en sus comienzos. Sin embargo, aun en el día de hoy muchos sistemas prepagados de salud, no consideran estas evaluaciones como entidades costo-efectivas en el tratamiento de pacientes. El Plan Federal de Salud Medicare, tiene aun en sus estatutos nacionales el no pagar por pruebas de exploración. No es hasta el año 1997, cuando el sistema federal comienza a entender que una onza de prevención es más efectiva económicamente que muchas libras de tratamiento.

Así comienza Medicare al final de este siglo a entender que la Educación en Diabetes, evaluaciones ginecológicas y pélvicas en la mujer, pruebas de antígeno específico prostático, (PSA), tienen una relevancia mayor en la capacidad de tratamiento.

Mirando hacia el futuro para el 2010 ó 2020, cuando del mapa del genoma humano sea completamente establecido, seremos capaces de poder diagnosticar enfermedades no sólo en sus comienzos como en el momento actual estamos haciendo, sino muchísimo más temprano. ¡Diagnosticaremos enfermedades antes de que éstas ocurran!

Ejemplo de ésta sería el poder predecir, basado en el esquema genético de una persona, si dicho individuo habrá de desarrollar diabetes en años próximos. De tener esta persona el defecto genético que apunte hacia la diabetes, podríamos comenzar el tratamiento de esta enfermedad mucho antes de que la anormalidad glucémica ocurra y por ende, mucho antes de que esta enfermedad afecte órganos como la retina, el riñón, el sistema nervioso periférico y el sistema vascular. Por otro lado en una familia en donde se hayan dado casos de enfermedad de "alzheimer", el poder determinar que ese sujeto no está genéticamente marcado para desarrollar esta enfermedad le ahorraría a ese individuo años de angustia y de incertidumbre pensando que como sus familiares, él puede estar marcado para desarrollar la enfermedad. El escrutinio en las mujeres predispuestas genéticamente para desarrollar cáncer de mama sería más intenso con el fin de determinar, a una etapa bien temprana, el comienzo de esta entidad clínica.

Por otro lado la ingeniería genética y la manipulación de las células primarias harán posible la creación de órganos y sistemas fabricados en el laboratorio con miras al reemplazo de estructuras dañadas. Estas manipulaciones de células primarias no son el producto de ciencia ficción, en la actualidad, por este método se están produciendo estructuras tan dispares histológicamente como huesos, vasos sanguíneos y músculos. De todos en bien conocido la creación de células sanguíneas a través del transplante en seres humanos genéticamente compatibles (HLA). De hecho n Puerto Rico ya hace algún tiempo que este proceso se está realizando. La cosecha de órganos, para reemplazo de una especie a otra, ha salvado en este momento las mayores dificultades de rechazo, quedando solamente problemas de orden ético e infecciosos.



Demás está decir que en el orden de cambios, la revolución habida en la última década referente a la forma de pago por los servicios médico-hospitalarios han trastocado la forma tradicional en que se ha practicado la medicina a través de gran parte de nuestro siglo.

Debido a estos elementos fundamentales la clase médica tiene por obligación que mantenerse unida; debemos y tenemos que dejar a un lado los mezquinos intereses personales y las trivialidades narcisistas, que solo nos servirán de freno a la capacidad de nuestra clase profesional, para poder influir y ser timón en las decisiones éticas, políticas y económicas relacionadas con la medicina en los años venideros a tenor con los cambios drásticos que habrán en la práctica de nuestra profesión.

Más que nunca los médicos debemos mirar el bosque y el horizonte y desviar nuestra visión de los cuatro o cinco árboles que tenemos a nuestro alrededor y que nos limitan nuestro entendimiento.

La principal razón de nuestra profesión es el cuidado del enfermo y la prevención de enfermedades. No permitamos que elementos foráneos a nuestra misión hipocrática sean quienes hagan las decisiones más importantes basadas en fines económicos y políticos, que sea la clase médica quien sirva de timón para dirigir el derrotero de nuestra práctica.

¡Esos son mis mejores deseos!

La Ciencia ante el Crimen
(Estudios Médico Legales)

Editorial Boletín Asociación Médica de Puerto Rico

Por: M. Quevedo Baez

¿Puede pensarse en una fisiología del crimen? Admitiendo, que todo acto es el resultado de una vibración inicial, en qué momento psíquico se producirá aquella, que haya de determinar el acto criminal?

Si es una vibración; ¿qué trayectoria ha seguido; dónde tomó el primer impulso y dónde se manifestó en acto?

Todavía anda la Fisiología, huérfana del conocimiento de aquello íntimo y misterioso, que se fragua en las entrañas de una célula. La ciencia no ha podido ir más allá de donde alcanzan los potenciales del microscopio. Hasta allí, todo es de su dominio: la física de su construcción, su forma, su textura, su composición química. Pero a la Fisiología le falta aun conocer su dinamismo psíquico; aquello que huye de las perspectivas del campo visual; aquello, que existiendo en la realidad, viviendo en ella, latiendo en la propia vida, no puede delinearse en la platina de los microscopios!

¡Qué ondas invisibles agitarán el complicado mundo de una célula, venidas de otras células preexistentes, originarias de otro u otros organismos, donde recibieron el impulso inicial!

Puesto que ninguna fuerza puede perderse en la mecánica del Universo, esas fuerzas, que en esas ondas circulan, no pueden agotarse, sin producir un trabajo. ¿Cuál de esas fuerzas, en esas invisibles ondas agitadas, será la del crimen?

He aquí planteado el problema, ante el cual el pensamiento de los legisladores deben detenerse, para no perseguir el delito o el crimen como un hecho, sin antes haber dirigido los esfuerzos todos de la moral social, a rectificar esas fuerzas, a modificar sus direcciones, a desviar su cauce.

Los Códigos no deben pararse sólo ante el delito; porque si su misión es la de moralizar, refrenando las desviaciones del sentido moral, convertidas en vicios y en crímenes, jamás cumplirán su objeto. Llegarán siempre tarde a sorprender el delito; es decir, cuando llegaron a su fin las fuerzas, que entrañaban el propio delito.

(Continúa en la pág. 107)

El Boletín y su Historia:

Todo acto de la vida es el resultado de una función previa, que se realiza en lo íntimo de la naturaleza. Aun los actos del pensamiento son funciones preexistentes.

Cuando el hombre piensa, en su cerebro se ha articulado, se ha expresado aquel acto del pensar.

Y ¡qué lenguaje sutil será aquel que dio lugar a que se convirtiera en pensamiento la vibración profunda del cerebro!

El crimen es la vibración final de una onda iniciada. Existe pues, un dinamismo que produce el acto criminal: hay pues, una fisiología del crimen.

Este no es más que la determinación fatal de una fuerza, que priva en el sujeto. Cuando este iergue su brazo para hundir el puñal en la entraña de una víctima, ha ido ciego y fatalmente, conducido y empujado para realizar tal acto, por invisibles e imperiosas fuerzas de su naturaleza. Su organismo las condensó y guardó, hasta que, en un momento inconsciente, para el sujeto, explotaron. Debieron explotar y lo hicieron, sin unidad de tiempo ni de lugar previsto, ni fijado por aquel.

Fuerza fue, que recibió, trasmitida por las leyes precisas y despóticas de la herencia y las guardó latentes para producirlas en un momento fatal de su vida.

Ante estas consideraciones, parecen conmoverse los fundamentos de todos los Códigos actuales, cuyas inspiraciones deben seguir al pie de la letra el proceso de formación de la criminalidad, tal como la ciencia lo estudia y considera.

A la conciencia de la sociedad pertenece el interesantísimo papel de rectificar, en el porvenir, todos los errores en que, hasta la fecha, han informado su moral de Códigos.

Si hay una fisiología del crimen, deténgase, ante ese hecho, los legisladores para prevenir los crímenes y sanear de mal tan profundo a la sociedad.

Que no sea un morbosismo social incurable el que resulte de sostener nutridos de errores, los Códigos escritos en nombre de la ley.

Allí donde la ciencia afirma un principio, debe empezar la virtud de la ley y sobre ella erigir todo bien social.

Estudios Originales:

Reliability of Serum Magnesium Values During Diabetic Ketoacidosis in Children

Julio Bauza, MD; Juan Ortiz, MD; Mazen Dahan, MD
Marcos Justiniano, MD; Rebecca Saenz, MD; Michael Vélez, MS

Key Words: *Magnesium, Hypomagnesemia, Magnesium depletion, Magnesium deficiency, Metabolic acidosis, Insulin dependent diabetes mellitus, Diabetic ketoacidosis.*
Abbreviated title: *Serum magnesium in diabetic ketoacidosis.*

Abstract

Objective: *To determine the prevalence of hypomagnesemia in diabetic children during diabetic ketoacidosis and following restitution of acid-base balance.*

Methods: *Eight consecutive diabetic children, ranging in age from 8 to 16 years, hospitalized in the pediatric intensive care unit with diabetic ketoacidosis from October 1st. through December 31st, 1995. A control group of 33 metabolically stable diabetic children, and a control group of 30 healthy children. Both control groups were similar in composition regarding age and sex to the study group. None of the patients in the study group and none of the controls had Magnesium supplementation given to them during the study period.*

Measurements*: Total serum Magnesium concentrations were measured from peripheral venous blood in all 71 patients. For the study group serum Magnesium was determined in a serial fashion:*

1. *upon admission in diabetic ketoacidosis*
2. *24 hours after admission*
3. *72 hours after admission*

Results*: The prevalence of hypomagnesemia was 62.4% in patients with diabetic ketoacidosis, (Group 1), 25% in patients after partial correction of ketoacidosis, (Group 2), and none in patients after resolution of ketoacidosis, (Group 3).*

The prevalence of hypomagnesemia was 6% for the chronic, metabolically stable diabetic control group, (Group 4), but 0% for the non-diabetic control group, (Group 5).

Average serum Magnesium levels were significantly lower (p less than 0.05), in patients admitted in diabetic ketoacidosis compared to those of both the diabetic and the non-diabetic control groups.

Also average serum Magnesium levels were significantly lower (p less than 0.05), in patients with corrected diabetic ketoacidosis than those of the healthy control group. But there were no significant differences (p=0.59263) in average serum Magnesium levels between the diabetic control group and the diabetic patients after resolution of ketoacidosis.

Conclusions*: In this study the prevalence of hypomagnesemia was documented to be higher than the average described elsewhere for pediatric, adult, and coronary intensive care units.*

As hypomagnesemia is an indication of Magnesium depletion, we speculate that the transient hypomagnesemia detected in our study group is an expression of a state of Magnesium depletion that is masked by correction of acidosis and the Magnesium shifts associated with it. Consequently serum Magnesium values ought to be considered most reliable during and not after correction of diabetic ketoacidosis. Since Magnesium was not supplemented to any of our patients, the normalization of their serum values must be the result of:

a. *decreased glycosuria-related urinary losses*
b. *cessation of acidosis-related urinary losses*
c. *Magnesium shifts from intra to extracellular space*

The high prevalence of hypomagnesemia and the significant lower average serum Magnesium levels in children with diabetic ketoacidosis reveals the magnitude of the problem and the potential for Magnesium depletion that occurs in diabetic children.

INTRODUCTION

Hypomagnesemia, Magnesium depletion, and Magnesium deficiency are common findings in critically ill patients (1,2). The physiology of Magnesium homeostasis is not fully known and it may be inefficient during periods of excessive losses of Magnesium (3,4). Among the causes of hypomagnesemia in children are genetic diseases, inadequate dietary intake, disturbed intestinal absorption, acute alcoholism, the use of diuretics and nephrotoxic drugs, and uncontrolled insulin dependent Diabetes Mellitus. Diabetes Mellitus can result in Magnesium wasting especially during periods of decompensation, and Diabetes Mellitus is the most frequent chronic disease associated with hypomagnesemia (5,6).

From the Ponce University Hospital and Ponce School of Medicine, Ponce, Puerto Rico
Principal Investigator address for correspondence:
Julio Bauzá, MD, 509 Tintillo Road, Tintillo Hills Guaynabo PR 00966

NO NECESITAS CONEXIONES

PARA TENER TELEFONO EL MISMO DIA

HOMEPHONE

PARA LA CASA

BUSINESSPHONE



Servicio telefónico inmediato que funciona con electricidad o baterías (opcionales). Llama ahora al **717-9500** o visita nuestras Tiendas o Kioskos.



El QCT 1200 y su tecnología digital CDMA son desarrollados por Qualcomm.



TU NUEVA COMPAÑIA DE TELEFONOS • 717-9500

Among the proposed mechanisms of Magnesium expenditure in Diabetes Mellitus and diabetic ketoacidosis are decreased intestinal absorption, increased urinary losses via osmotic drainage of Magnesium molecules due to glycosuria, and impaired renal absorption (7).

The objective of the present study was to determine the prevalence of hypomagnesemia during and after correction of diabetic ketoacidosis in order to elucidate Magnesium homeostasis.

We are not aware of a previous study in pediatric diabetic patients where serum Magnesium levels were determined in an analogous fashion.

METHODS

A population of 71 children was studied; of these 8 were children admitted to the PICU with the diagnosis of diabetic ketoacidosis, 33 were metabolically stable diabetic children followed at the Pediatric Endocrinology Clinic, and 30 were non-diabetic normal children without known risk factors for hypomagnesemia or Magnesium deficiency. The control groups were similar in composition regarding age and sex of the subjects.

Upon enrollment, PICU patients were questioned and examined to identify the presence of symptoms of hypomagnesemia; specifically gastro-intestinal (nausea, vomiting), neuromuscular (myasthenia, tetany seizures), neuro-psychiatric (Glasgow coma scale), and cardiovascular (arrhythmia, systemic hypertension).

After obtaining an informed consent, venous blood samples were drawn in a serial fashion: upon admission, after 24 hours , and after 72 hours. Among the variables serially determined in the study group were: venous blood gases, plasma acetone, blood sugar, serum electrolytes, Magnesium, Calcium, and urinalysis. Glycated hemoglobin was determined once. Control patients (both diabetic and healthy controls) had a single venous sample for serum Magnesium. No Magnesium supplementation was allowed during the study period provided that patients did not present clinical evidence of Magnesium deficiency.

The agreed definitions were: 1) Normal total serum Magnesium: 1.6 to 2.3 mg/dl, 2) Hypomagnesemia: below 1.6 mg/dl, and 3) Diabetic ketoacidosis as metabolic acidosis with decreased blood pH (below 7.30), decreased pCO2 (below 40 mm Hg), and decreased bicarbonate (below 23 mEq/L), associated to hyperglycemia, ketonemia, glycosuria, and ketonuria (10). Partial correction of diabetic ketoacidosis was present when the measurements for pH, pCO2, and bicarbonate were improved from the initial determination but they still remained below the lower limit of normal and ketonemia although improved was still present. The study was conducted at the Ponce University Hospital a general, tertiary care hospital and was approved by the I.R.B. Consecutive enrollment of patients lasted 3 months (October 1 through December 31, 1995).

Differences in the means between groups was tested by using analyses of variance. All differences are statistically significant at $P < .05$ or less. The analyses were conducted with SPSS version 7.0.

RESULTS

Non-specific gastrointestinal symptoms were present in all patients from the study group but none of them had clinical criteria for hypomagnesemia.

The serially determined serum Magnesium values in 8 diabetic ICU children and pertinent patient profile data are presented in Table I. Average, standard deviation, and median values for serum Magnesium concentration and the prevalence of hypomagnesemia for the five groups are presented in Table II.

The average serum values for Magnesium, pH, pCO2, bicarbonate, blood sugar and acetone are presented in Table III. ANOVA (p values) for comparison of average serum Magnesium values for the 5 groups are presented in Table IV.

DISCUSSION

A previously unreported observation of transient self-correcting hypomagnesemia during diabetic ketoacidosis is presented. The significantly low average serum Magnesium levels found in patients during diabetic ketoacidosis and the fact that the prevalence of hypomagnesemia in these patients turned out to be higher than the average described at intensive care units elswhere points to the magnitude of the problem and to the potential for Magnesium depletion that occurs in diabetic children (1, 11).

Serum Magnesium values are difficult to interpret as it has been demonstrated that depleted intracellular stores can be associated with normal serum Magnesium levels (12, 13). However, the widely accepted notion that hypomagnesemia is always an indication of Magnesium depletion (14) allows for the speculation that the transient hypomagnesemia detected in the study group is an expression of a state of depletion which is masked by the correction of acidosis and the Magnesium shifts associated with it. Consequently, serum Magnesium values would be most reliable during and not after correction of diabetic ketoacidosis.

TABLE I
SERUM MAGNESIUM VALUES IN EIGHT DIABETIC CHILDREN DURING DKA AND AFTER RECOVERY AND OTHER SELECTED CHARACTERISTICS

NUM	AGE (YEARS)	SEX	DURATION OF DIABETES (YEARS)	NUMBER OF HOSPITALIZA-TIONS IN DKA	% GLYCATED HEMOGLOBIN	GROUP 1	GROUP 2	GROUP 3
1	16	F	6	14	20.0	2.2	1.7	1.9
2	8	M	1	2	8.2	1.8	1.4	1.9
3	15	M	4	0	14.8	1.5	2.2	2.0
4	14	F	6	0	13.5	1.4	1.8	1.9
5	14	F	9	10	19.0	2.0	1.5	1.8
6	14	M	3	12	8.4	1.2	2.0	1.6
7	14	F	9	2	9.5	1.5	1.8	1.6
8	9	M	0.75	0	13.0	1.5	1.7	1.9

DKA: Diabetic Ketoacidosis

GROUP 1: Diabetic ketoacidosis, upon admission
GROUP 2: 24 hours after admission
GROUP 3: 72 hours after admission

TABLE II
SERUM MAGNESIUM VALUES (MG/DL), AND PREVALENCE OF HYPOMAGNESEMIA FOR THE FIVE GROUPS.

GROUPS	1	2	3	4	5
NUMBER OF PATIENTS	8	8	8	33	30
AVERAGE	1.64	1.76	1.83	1.87	2.19
STANDARD DEVIATION	0.33	0.26	0.15	0.22	0.17
MEDIAN	1.50	1.75	1.90	1.80	2.20
PREVALENCE OF HYPOMAGNESEMIA	62.5%	25%	0.0%	6.0%	0.0%

GROUP 1: Diabetic Ketoacidosis, upon admission.
GROUP 2: 24 hours after
GROUP 3: 72 hours after
GROUP 4: Diabetic controls
GROUP 5: Normal controls

It can also be argued that Magnesium losses in diabetic ketoacidosis are so severe that homeostasis cannot be restored prior to normalization of acid-base balance and that the observed transient hypomagnesemia has probably little significance. But the fact that 5 patients who were initially hypomagnesemic and 2 other patients whose hypomagnesemia was detected 24 hours after admission, became all normomagnesemic 72 hours after their admission in diabetic ketoacidosis, even when no Magnesium supplementation was administered, allows for the assumption that a combination of factors like cessation of gastrontestinal and urinary losses, plus a shift of Magnesium from cell reservoirs are responsable for this correction. Since no measurements of intracellular Magnesium were obtained in this study, we are not able to validate or deny our previous conclusions.(*)

The present data contrasts with those of other investigators where transient hypomagnesemia in non diabetic patients appeared after correction of acidosis. The assumed exit of Magnesium from the cell would explain the presence of normomagnesemia during acidosis (15, 16).

TABLE III
AVERAGE VALUES FOR SERUM MAGNESIUM, PH, PCO2, BICARBONATE, BLOOD SUGAR AND PLASMA ACETONE FOR THE THREE GROUPS.

	GROUP 1	GROUP 2	GROUP 3
NUMBER OF PATIENTS STUDIED	8	8	8
SERUM MAGNESIUM	1.64	1.76	1.83
pH	7.16	7.33	7.35
pCO2	32.1	38.7	40.7
BICARBONATE	11.8	22.2	22.8
BLOOD SUGAR	335.4	294.0	268.6
PLASMA ACETONE	MODERATE	TRACE	NEGATIVE

TABLE IV
ANOVA (P VALUES) FOR COMPARISON OF AVERAGE SERUM MAGNESIUM VALUES FOR THE FIVE GROUPS

	P VALUE	
GROUP 1 VS. GROUP 4	LESS THAN 0.05	0.01868
GROUP 1 VS. GROUP 5	LESS THAN 0.05	0.00000
GROUP 3 VS. GROUP 4	NON SIGNIFICANT	0.59263
GROUP 3 VS. GROUP 5	LESS THAN 0.05	0.00004
GROUP 4 VS. GROUP 5	LESS THAN 0.05	0.00000

Larger studies are needed where simultaneous determination of extracellular and intracellular Magnesium is undertaken for a better understanding of the Magnesium puzzle. Serum Magnesium levels should be routinely determined in diabetic patients, especially during diabetic ketoacidosis and systemic Magnesium supplementation should be implemented whenever symptomatic hypomagnesemia is detected. (*)

The fact that all 8 ICU patients had abnormally high levels of Glycated hemoglobin, and also the finding that 5 out of 8 ICU patients had a history of at least 2 previous admissions in diabetic ketoacidosis suggests that poor diabetic control and hypomagnesemia go hand in hand.

REFERENCES

1. Ryzen E. Magnesium homeostasis in critically ill patients. Magnesium 1989; 8: 201-202.

2. Salem M, Muñoz R, Chernow B. Hypomagnesemia in critical illness; A common and clinically important problem. Crit Care Clin 1991; 7:225-252.

3. Ryan MF. The role of magnesium in clinical biochemistry: An overview. Ann Clin Biochem 1991; 28: 19-26.

4. Rude RK. A symposium: magnesium deficiency-pathogenesis, prevalence and strategies for repletion. Am J Cardiol 1989; 63: 31G-34G.

5. Rohn RD, Pleban P, Jenkins LL. Magnesium, zinc and copper in plasma and blood. Cellular components in children with IDDM. Clin Chem Acta 1993; 215-218.

6. Nadler JL, Rude RK. Disorders of magnesium metabolism. Endocrinol Metab Clin North Am 1995 sep; 24: 623-41.

7. Roffi M, Kanaka C, Mullis PE, Peheim E, Bianchetti MG. Hypermagnesiuria in children with newly diagnosed insulin-dependent diabetes mellitus. Am J Nephrol 1994; 14: 201-206.

8. Schnack CH, Bauer S, Bauer I, Pregant P, Hopmeier P, Shernthaner G. Hypomagnesemia in type 2 diabetes mellitus is not corrected by improvement of metabolic long term control. Diabetologia 1992; 35: 77-78.

9. Altura BM, Altura BT. Role of magnesium in the pathogenesis of hypertension: Relationship to its actions on cardiac, vascular smooth muscle, and endothelial cells updated. In: Laragh JH and Brenner BM, eds. Hypertension: Pathophysiology, Diagnosis, and Management, 2nd. Edition, New York, Raven Press, 1995.

10. Berhman RE, Kliegman RM, and Arvin AM. Nelson Textbook of Pediatrics. 15th ed. Philadelfia, W.B. Saunders Co. 1996.

11. Ryzen E, Elkayam U, Rude RK. Low blood mononuclear cell magnesium in intensive cardiac care unit patients. Am Heart J 1986; 11: 475-480.

12. Ralston MA, Murmane MR, Kelly RE et al. Magnesium content of Serum, circulating mononuclear cells, skeletal muscle and myocardium in congestive heart failure. Circulation 1989; 80: 573-580.

13. Bauza J, Mercado C, Vélez M. Magnesium content of peripheral blood lymphocytes: Prevalence of magnesium depletion in the pre-term and other high risk infants. (Abstract) VI Congreso Latino de Cardiología Pediátrica Puerto La Cruz, Venezuela 1994; P42.

14. Dyckner T, Wester PO. Magnesium deficiency-guidelines for diagnosis and substitution therapy. Acta Med Scand (suppl) 1982; 661: 37-41.

15. Kristiansen VB, Larsen J, Nielsen TC. Correlation of respiratory acidosis and transient hypomagnesemia. Acta Med Scand 1985; 218: 133-135.

16. Cadwell J, Read G. Unreliability of plasma magnesium values in asphyxiated neonates. Magnesium 1989; 8: 11-16.

Estudios Originales:

Eleven Years Experience with the Medtronic Hall® Valve

Iván Ayala, M.D.; Pablo I. Altieri, M.D.; Efraín Defendini, M.D.
Héctor Banch, M.D.; Robert González, M.D.

Abstract: We are reporting our experience of eleven years with the Medtronic Hall® Valve. Four hundred twenty two patients received the valve with a mortality of 7.9%.

The decision of which valve to be used in certain patients depends on the individual needs of each patient including age and contraindications for the use of anticoagulation. An aspect which is of crucial impor-tance is the selection, the durability and complications of the valve.

Of the new generation valves, the Medtronic Hall® valve is probably one of the most durable one and compares with any valve [1-5]. It is the purpose of this manuscript to describe our experience with this valve and to compare the results to similar valves in use at the present time.

Materials and Methods: Description of the Valve:

The Medtronic Hall® valve is a pivotal disc valve, which consists of a pyrolytic carbon disc occluder, a polished titanium housing, and a knitted Teflon fabric sewing ring. There are no welds or introduced bends. The aortic valve disc opens to a full 75% opening angle and the mitral to 70%. The importance of this openings, is that it allows for maximum opening, even flow distribution on both sides of the open disc, reducing the risk of thrombosis and thromboembolic incidence. The elliptical shape, housing guide strut provides great strength, while reducing resistance to blood flow past its surface. Also, oval shapes in the blood stream reduce the potential for thrombus formation, more than round shapes projected across blood stream.

Patient Population:

Between December, 1981 and June, 1992, 422 patients received Medtronic Hall® valves. The mean age of the aortic patients was 47 years and of the mitral 32 years. All had full catheterization including right and left heart catheterization and coronary angiography when needed, the left ventricular function was studied in all. All underwent cardiovascular surgery using standard techniques. Thirty three of the patients had coronary disease requiring bypass surgery. The patients who had mitral valve replacement had mitral disease (insufficieny or stenosis) and the ones with aortic valve replacement had aortic stenosis or insufficiency. The ejection fraction of the patients was more than 30%.

Mitral Valve Surgery:

Mitral valve surgery was performed through a median sternotomy incision using general hypothermia and crystalloid cardioplegia. When the mitral valve is going to be inserted, the mitral annulus is divided into four equal quadrants by means of four mattress pledgetted blue sutures. The suture is drawn in from the atrial to ventricular side. The obturators are used to determine the correct valve size. The size of the ventricular cavity as well as the size of the annulus is considered in the selection of the mitral prosthesis. An obturator that provides a loose fit in the annulus that can be passed easily into the left ventricle, without impingement on the septum, is selected. The four quadrant sutures are passed through the selected valve sewing ring so that the large orifice is oriented posteriorly with the down-ward moving portion of the disc posterior, thereby dividing the sewing ring into four equal quadrants. Alternating white and green sutures are places in each quadrant. The valve is lowered making sure there is no entanglement of the sutures. The valve holder is removed and traction is placed by all the sutures. Valve function is tested making sure the ventricular muscle will not restrict the motion of the disc, which may cause improper function, arrhythmias, and thrombosis. Once the valve is in position and functioning properly, all sutures are tied starting with the four quadrant sutures. The valve is tested again

Department of Medicine and Surgery, University of Puerto Rico, Medical Science Campus
Address for Reprints:
Pablo I. Altieri, M.D.
Box 8387, Humacao, Puerto Rico 00792

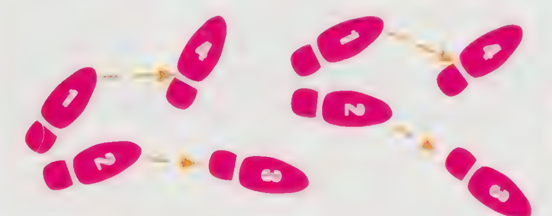
Toma un pasito hacia tu salud.

Si quieres mantener tu salud en armonía, escucha bien lo que te pide tu cuerpo. Puedes tomar la deliciosa bebida nutricional Sustacal como un suplemento nutricional, con tus comidas, meriendas o como sustituto de éstas. Sustacal te brinda:

- Rica fuente de energía con 15g de proteína en cada 8oz.
- 25 vitaminas y minerales
- Bajo en grasas saturadas
- Libre de colesterol
- Amplia variedad: líquido, pudín, polvo y con fibra
- Tres deliciosos sabores: Vainilla, Chocolate y Fresa

Toma un pasito hacia Sustacal.

Con la confianza de médicos y nutricionistas por más de 25 años.





SUSTACAL®
COMPLETE NUTRITION



reconfirming the adequate function. Positioning of the large orifice posteriorly guards against interference by the ventricular septum.

Aortic Valve Surgery:

The deformed valve is resected leaving only a 2mm rim of tissue. Any residual calcifications are carefully removed. The largest valve fits well in the aortic root is selected. Our policy is, that if we cannot accommodate a 21mm valve, a root enlargement is performed using standard techniques, which will include the aortomy incision that is extended through the commissure of the noncoronary and left cusp into the septal leaflet of mitral valve to enlarge the aortic annulus. Once a valve is selected, it is oriented in the valve holder so that the major orifice is oriented toward the noncoronary cusp area. We start our sutures on the right cusp area followed by the left cusp and finally the noncoronary cusp. The sutures are placed midway high in the sewing ring to prevent encroachment upon the coronary orifices, however, if they are too high they may interfere with free disc motion. Once all sutures are in place, they are made tight and the valve holder is the removed. The valve is seated with the index finger into the aortic foot annulus. The valve is tested for adequate function. If any tissue interferes with its motion, such as ventricular or aortic wall calcifications, the interfering tissue is removed and the valve is reoriented. Once adequate function is demonstrated, all the sutures are tied and cut closely to the knots, so that they remain below the valve housing.

Eight patients with Marfan Syndrome had a Medtronic Hall® valve inserted in a Dacron tube graft. This technique has been previously published.

Sex Distribution:

Table I shows the sex distribution of all patients. Of the 277 aortic valves, 86 were female and 141 male. In the mitral valve 156 were female and 57 were males. One male patient had a tricuspid valve replacement alone.

TABLE I
SEX DISTRIBUTION OF VALVE REPLACEMENTS

POSITION	PATIENTS	FEMALE	MALE
AORTIC	227	86	141
MITRAL	213	156	57
TRICUSPID	1	—	1
TOTAL	**441**	**242**	**199**

Valve Size:

Table II shows the sizes used in the aortic position. As seen both sexes, the most frequent size used was #21 (when #21 valve will not fit, then aortic r oot enlargement was done and a #21 valve was then reinserted), followed by #23 and #25. The lar ger sizes were the least used. We think, the use of smaller valve sizes is due to the fact that the aortic root of the puertorrican population, especially females, is smaller than the non puertorrican operated on.

TABLE II
DISTRIBUTION BY SEX AND SIZE
OF THE AORTIC VALVE REPLACEMENT

	SIZE	MALE	SIZE	FEMALE	TOTAL
1	#20	6	#20	27	33
2	#21	43	#21	35	78
3	#23	37	#23	14	51
4	#25	39	#25	6	45
5	#27	11	#27	2	13
6	#29	5	#29	0	5
7	#31	0	#31	2	2
		141		86	227

= Size of valve

Table III shows the valve sizes used in the mitral position. The most frequently used valve was #27 followed by #29 and #31.

TABLE III
DISTRIBUTION BY SEX AND SIZE
OF THE MITRAL VALVE REPLACEMENT

	SIZE	MALE	SIZE	FEMALE	TOTAL
1	#23	0	#23	2	2
2	#25	2	#25	29	31
3	#27	10	#27	74	84
4	#29	28	#29	34	62
5	#31	17	#31	16	33
6	#33	0	#33	1	1
		57		156	213

Table IV shows the double valve replacement performed. There were 29 patients. Thirteen were males and 16 females. The most frequent combination was a #21 in the aortic position and a #29 in the mitral position.

TABLE IV - A
DOUBLE VALVE REPLACEMENT
SEX AND VALVE NUMBER COMBINATIONS

Male = 13 patients

MITRAL	AORTIC
#27	#21
#29	#23
#29	#23
#27	#23
#29	#25
#29	#21
#31	#27
#29	#25
#31	#23
#29	#27
#27	#21
#31	#29
#25	#21

Female = 16 patients

MITRAL	AORTIC
#27	#23
#29	#25
#31	#21
#29	#21
#29	#21
#27	#21
#27	#21
#29	#23
#25	#21
#25	#20
#25	#21
#27	#23
#29	#25
#27	#21
#25	#21
#27	#23

Complications:

Table V shows the causes of early death (7.9%) and late deaths. As seen we haven't had a valve related death. The two most frequent causes of early death were patients who had complications due to renal failure. They were patients operated with renal insufficiency, who had severe bleeding during surgery, and sepsis (in patients operated with bacterial endocarditis). It is important to notice that we didn't have had any problems with clinically significant hemolysis or any severe embolic episodes. We have had only two cases of transient embolic episodes. No significant perivalvular leaks have been detected.

TABLE V

EARLY DEATH	LATE DEATH
1. Cardiac Tamponade	Congestive heart failure
2. Patients operated with Bacterial Endocarditis. Died in sepsis.	Operation for a pseudo aneurysm (case of Marfan's Syndrome)
3. Perforation of the left ventricular wall during surgery.	
4. Acute myocardial infarction postoperatively. Patients had minimal coronary disease prior to surgery and was not considered for coronary bypass.	
5. Unrecognized dislocation of the aortic annulus by a stab wound.	
6. Acute renal failure super-imposed in chronic renal disease.	
7. Severe bleeding during surgery.	
8. Brain ischemia.	

Follow-Up:

Most of our patients have been followed at a special anti-coagulation clinic. They are followed with monthly prothrombin time and serial echocardiograms and parameters to detect clinically important hemolysis. We have not experienced any valvular malfunction, thrombosis, or clinically important hemolysis. Only two episodes of transient brain embolism occurred without neurologic deficits. All of our patients have been in NYHA Class I or II postoperatively.

Conclusion:

Our experience for eleven years with the Medtronic Hall® valve has been excellent without valve failures. We think that our low rate of complications is due to the fact that our patients are followed monthly and the prothrombin time is kept 2.5 times the control. These results compares with any valve especially ST Jude being used at present in any surgical center.

Abstracto: *Estamos reportando nuestra experiencia de 11 años con la válvula Medtronic Hall®. Cuatrocientos veintidós pacientes la recibieron con una mortalidad de 7.9%.*

REFERENCES

. Hauge SN, Semb B. Abdal Noor MSC, Hall KV (1983) A 5-Year Experience with the Medtronic Hall Disc Valve Prosthesis Circulation 68; 169-174.

. Starek PJK, Murray GF, Keagy BA. Wilcox BR (1963) Clinical Experience with the Hall Pivoting Disc Valve Thoracic Cardiovascular Surgeon 31/ 11:66-68 New York: George Thieme Verlag Stuttgart.

. Beaudet RL. Pirier NC. Guerraty AJ. Doyle D. Fifty-Four Month Experience with an Improved Tilting Disk Valve (Medtronic Hall) Thoracic Cardiovascular Surgeon 31 11:89-93; New York: George Thieme Verlag Stuttgart.

. Semb B. Hauge SN. Hall KV Intraoperative and Postoperative Hemodynamic Studies in Patients Undergoing Aortic Valve Replacement with the Hall-Kaster Cardiac Kisc Prosthesis 27: 92-97, 1979, New York: George Thieme Verlag Stuttgart.

. Hall KV an Improved Pivotal Kisc Type Prosthetic Heart Valve Oslo City Hospital 29: 3-21, 1979.

. Jarvinen A. Vertanen K. Peltolak, Magmies T. Detonen P. Ko. Manni A., Postoperative Disc Entrapment Following Cardiac Valve Replacement - Report of Ten Cases Thoracic Cardiovascular Surgeon. 32: 152-156, 1984, New York: George Thieme Verlag Stuttgart.

. Chaux A. Gray RJ, Matloff JM, Feldman H. Sustaita H an Appreciation of the New St. Jude Valvular Prosthesis Journal of Thoracic Cardiovascular Surgery. 81: 202-211, 1981.

. D'Alessandro LC, St. Jude Medical Prosthesis; clinical Results, St. Jude Medical, Inc., Second Symposium, March 11-14, 1981, San Diego, California.

. Medtronic Blood Systems. Three-Year Clinical Evaluation of the Hall- Kaster Prosthetic Valve, 1980.

. Bjork VO. Holmgren A. Ovenfors CP Olinc Clinical and Hemodynamic Results of Aortic Valve Replacement with the Bjork-Shiley Tilting Disc Valve Prosthesis Scandinavian Journal of Thoracic Cardiovascular Surgery 5: 177-191. 1971.

. Pyle RB. Mayer JE. Lindsay WG. Jorgensen CR. Wang Y. Wicolof DM Hemodynamic Evaluation of Lillehey-Kaster and Starr-Edwards Prosthesis And Thorac Surg 76: 336-343. 1978.

. Forman E. Gersh B. Fraser R. Beck W. Hemodynamic Assessment of Lillehei-Kaster Tilting Disc Aortic and Mitral Prostheses Journal of Thoracic Cardiovascular Surgery 75: 595-598. 1978.

. Horstkotte K. Haerten K Herzer JA. Seipel L. Bircks W. Loogen F Preliminary Results in Mitral Valve Replacement with the St. Jude Medical Prosthesis: Comparison with the Bjork-Shiley Valve Circulation. 64.II: 203-209. 1981.

. Yogahattan AP. Woo YR. Williams FP in Vitro Hydrodynamic Characteristics of the St. Jude Bileaflet Prosthesis Advances in Cardiac Valves. De Bakey Med., New York Medical Books, 1982.

. Bradley LM. Derry LW, Watson DC'Failure of St. Jude Medical Mitral Prosthesis Diagnosed by Two-Demiensional Echocardiography Am J Cardiol 57: 1385, 1984.

. Tull R Complications of Convexo-Concave Heart Valve Devices and Diagnostic Letter 12:8, 1985.

Vol. 90 • 7-8-9-10-11-12 / 1998 • Pág. 117, 120

Estudios Originales:

A Mini-invasive Approach to Transduodenal Sphincteroplasty

Victor M.Carlo, Gerhart Ramirez Schon, Edwin Soler Candelaria
Ponce School of Medicine, Ponce Puerto Rico

Summary: *A right lumbar approach to the duodenum was developed to perform transduodenal sphinctero-plasty for the treatment of retained common bile duct stones. With experience, the procedure was reduced to a mininvasive approach. Nine patients with symptomatic choledocal stones were subjected to translumbar transduodenal sphincteroplasty. Eventually it became obvious that limited dissection was equally effective in exposure of pertinent anatomical structures and ease of performance. Four patients were intervened using the mini-invasive approach. In one instance the procedure was combined with laparoscopic cholecystectomy and cholangiogram. There was no mortality or morbidity and there was universal clearance of the common bile duct.*

Introduction

The great acceptance of endoscopic sphincterotomy during the past five years defines the etiologic site of retained choledochal stones where it truly is, in the sphincter of Oddie. Despite the advantages of endoscopic sphincterotomy (ES) shortcomings have become apparent. Availability is not universal. Skilled endoscopists tend to occur in large urban centers and may not be available to the indigent population. Duct clearance is not universal in endoscopic sphincterotomy, requiring multiple procedures in many patients. The greater the initial duct clearance the greater the complications, thus the tendency to increase the sphincterotomy in small increments until clearance is obtained (1, 2, 3, 4). The literature does not document the frequency of repeat ES, but occasional failures occur in all settings (1). The mortality of ES is generally reported as 2%, which is the same as that reported in unselected patients for open transduodenal sphincteroplasty (5).

Transduodenal sphincteroplasty has not recruited a large following among American surgeons, perhaps because they tend to equate duodenotomy with the dire complications of duodenal closure in peptic ulcer disease. We have a ten-year prospective study with more than 400 unselected patients on whom transduodenal sphincteroplasty with a mortality of less than 2%, no duodenotomy rupture and 100% duct clearance on the first and only intervention. This study which introduces a mininvasive approach is an attempt to reduce the invasiveness of the procedure, approximating the benefits of the laparoscopic approach. We have a long-term goal of converting it to an endoscopic procedure.

Materials and Methods

During the past six years we have developed a lumbar approach for transduodenal sphincteroplasty. This approach has been reduced to a mininvasive procedure in the last five patients.

The Operation: The patient is slightly inclined to the left by means of roll placed under the lumbar region so a 5 cm. incision can be performed at the junction of the 9th and 10th costal cartilages (Fig. 1). A headlight

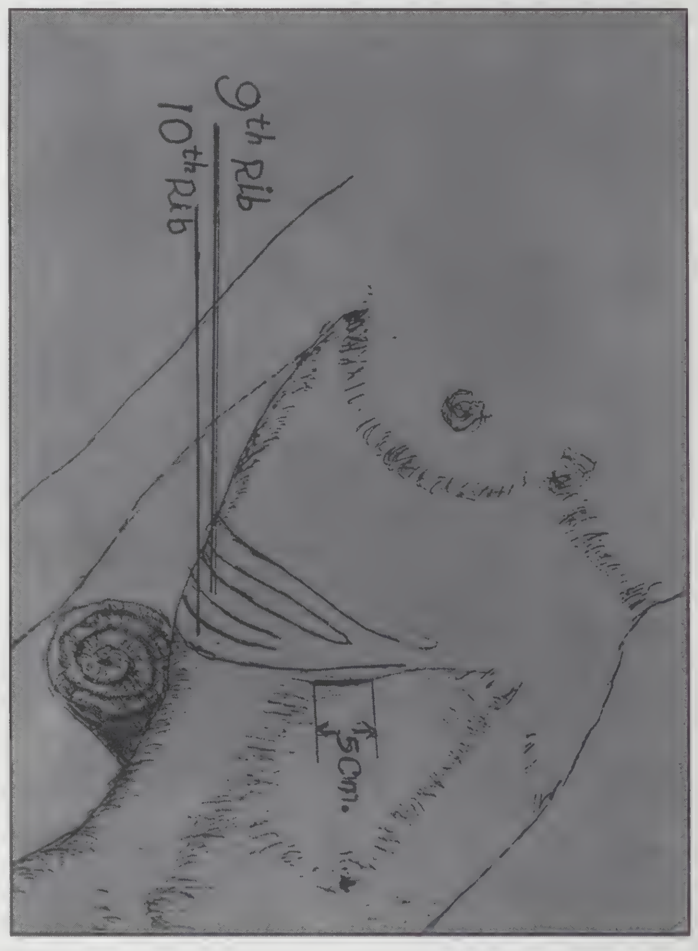


Fig. 1

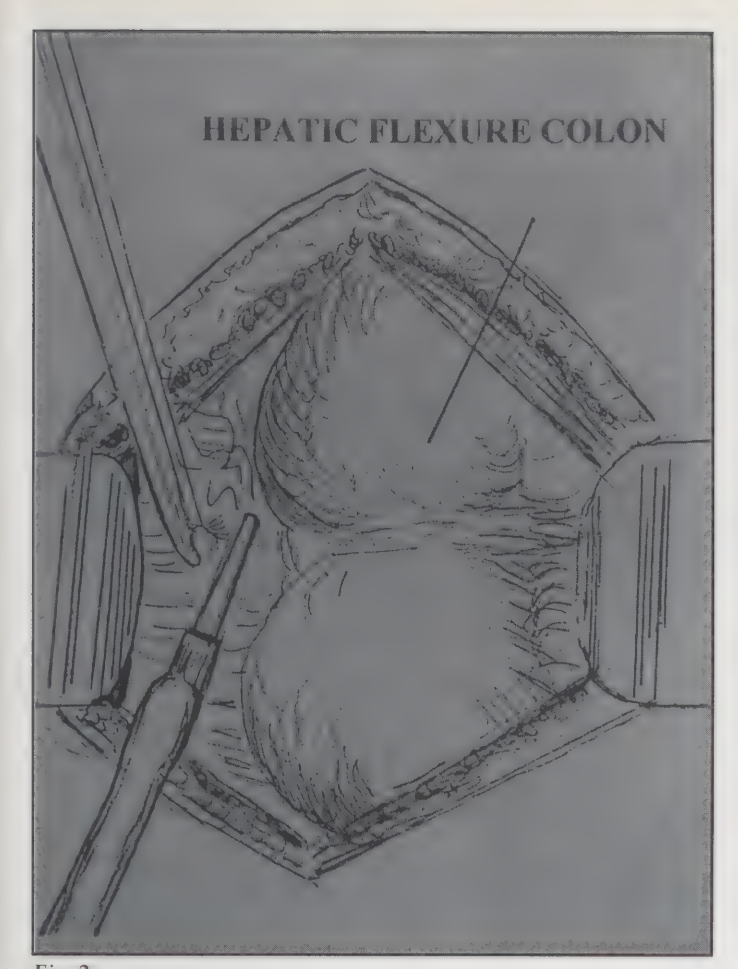


Fig. 2

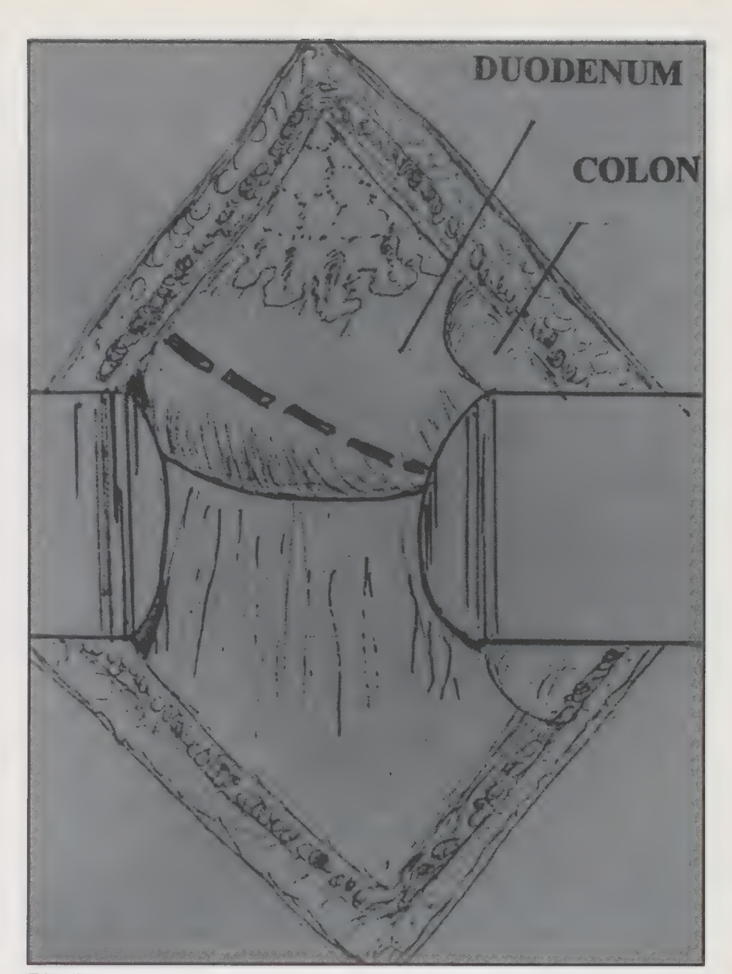


Fig. 3

is almost essential, as the small wound will not permit the beam from the operating room lamplight to enter the wound. The external oblique muscle is sectioned and the internal oblique and transversus abdominis muscles are opened along the course of their fibers. The retroperitoneal fat is entered and the hepatic flexure of the colon identified. The hepatic flexure is dissected and retracted caudaly and the duodenum is exposed. The duodenum is dissected extraperitoneally and opened along diagonal line that bisects it at the exposed segment. Two 2.5 cm. Deaver retractors are inserted in the duodenum and pulled away from each other and towards the surface of the wound. The retracted duodenum can be brought 3 to 4 cm. from the skin edges. If the procedure is being performed with laparoscopic cholecystectomy, a catheter that has been inserted into the cystic duct, through the common duct into the duodenum identifies the sphincter of Oddi for subsequent sphincteroplasty. If it is performed for retained stones and there is no control of the cystic duct, one must identify the papilla by intraduodenal palpation, a method that hardly ever fails, once one has gained experience. If this should fail, visual inspection of the duodenal mucosa adherent to the pancreas will identify a small orifice where bile or pancreatic fluid emanates. When there is no catheter in the common bile duct identification of the papilla is the most time consuming step of the procedure. Once the papilla is identified an 8 French catheter is inserted into the common bile duct antidromically, not only to identify the papilla without a doubt, but also to define the trajectory to follow in opening the duodenum to construct the sphincteroplasty. Once the papilla is identified the procedure goes at a fast pace. The papilla is opened along the course of the catheter (Fig. 4). Sutures approximating the mucosa of the common duct and the duodenum are placed with care to avoid the pancreatic duct, that is readily identified at the opposite wall of the opened sphincter (Fig. 5). The sphincteroplasty is complete when the common duct can be visualized with ease through the opened sphincter and the largest Hegar dilator accepted by the common bile duct can be passed retrogradely from the duodenum with ease. Extraction of the stones is not essential, as the stones will spontaneously migrate to the duodenum by means of the bile flow, never the less, a serious effort to remove the stones should be done with the most appropriate of the paraphernalia available that has been developed for this intraoperative maneuver.

Results

We have performed trans-lumbar transduodenal sphincteroplasty in ten patients ranging in age from 16 to 52 years, with an average of 30 years. All but

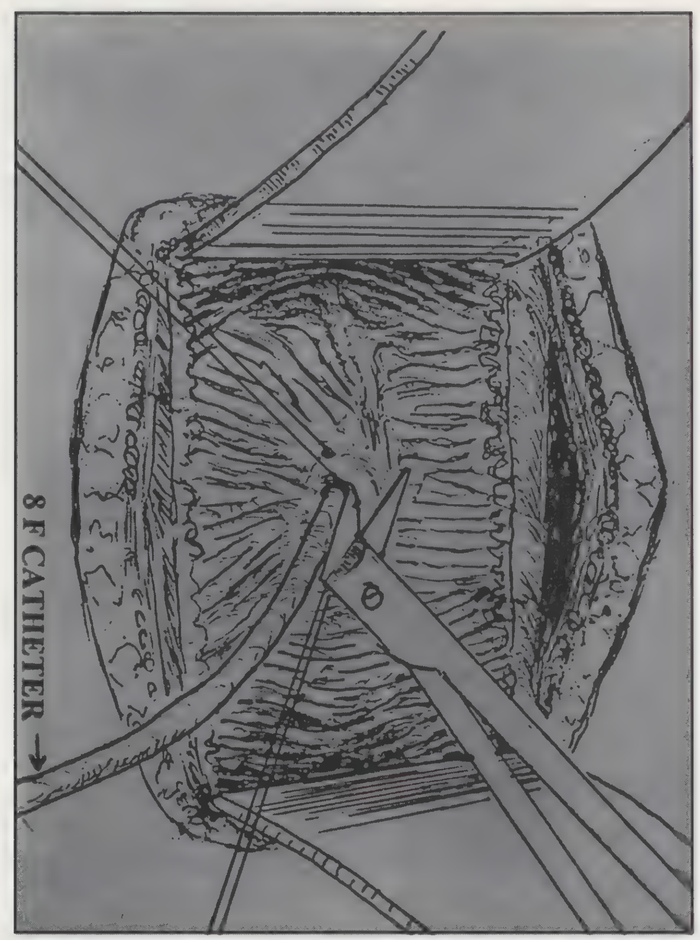


Fig. 4

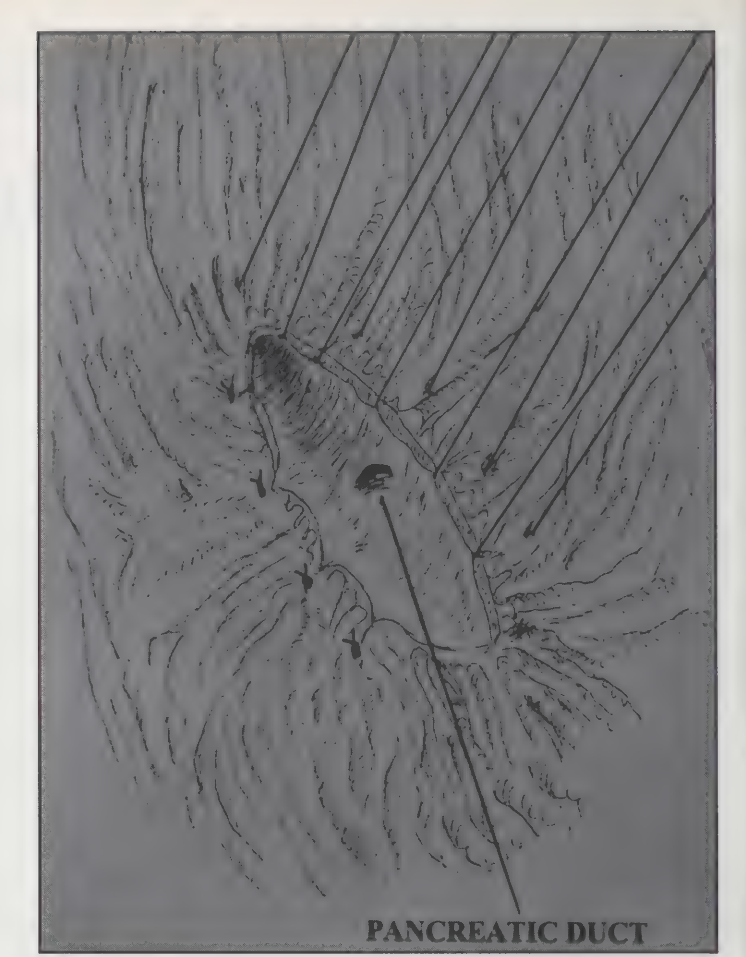


Fig. 5

one was female. All had complete duct clearance as proved by an uneventful postoperative follow up, with normal bilirubin and alkaline phosphatase levels, of over six months in every case. The post operative hospital stay was 4.7days on the average and there were no deaths or complications.

Discussion

Endoscopic sphincterotomy is of great utility, as its popularity proclaims. In the United States transduodenal sphincteroplasty is used as complementary to endoscopic sphincterotomy. When the endoscopic procedure fails, the general surgeon is called to solve the problem. ES fails in 10 to 20 % of the cases treated (1,9) although some reports argue this point (2). Extraordinary results in ES have been reported from the most prestigious university practices, but it is debatable whether these statistics can be supported by community practices (6).

In the absence of strictures of the common bile duct, TS is, in our opinion, the best choice. The other alternatives are choledochoenterostomy. It has results similar to TS but has a 3% incidence of the ìsump syndromeî as a late sequela (7, 8). This syndrome is reportedly caused by accumulation of debris in the defuctionalized distal common bile duct that suppo-

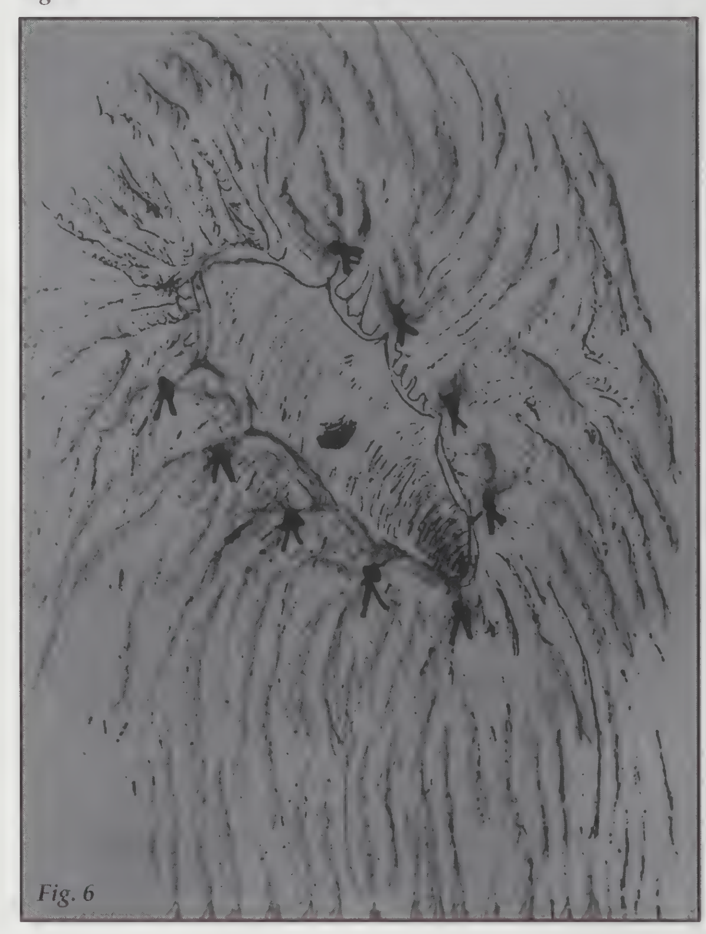


Fig. 6

sedly causes cholangitis and septic manifestations, but this could be caused by stenosis of the choledocho-enterostomy.

Our initial attempt to reduce the invasiveness of TS appears to go in the right direction. The five patients presented illustrate the safety and feasibility of a procedure whose technical details have been resolved. We plan to further reduce the invasiveness of TS until operative trauma is comparable to the endoscopic and laparoscopic surgery.

REFERENCES:

1. Lambert ME, Betts CD, Hill J, Faragher EB, Tweedle DE: Endoscopic sphincterotomy; The whole truth. Br J Surg 1991; 78: 473-476.

2. Cerny J, Vavrecka J: Vyznam intervencnej endoskopie v chirurgii zlcovych ciest. Rozhl Chir1990; 69: 144-147.

3. Vaira D, DíAnna L, Ainley C, Dowsett J, Williams S, Baillie J, Cairns S, Croker J, Salmon P., Cotton P, and others: Endoscopic sphincterotomy in 1000 consecutive patients. Lancet 1989; 2(8660): 431-434.

4. Ginestal-Cruz A., Grima N., Correia AP, Duarte V., Correia J.P.: Esfinterotomia endoscopica na coledocolitiase: Analise de una experiencia de 530 intervencoes, Acta Med.Port.1990; 3:133-140.

5. Ramírez Schon G, Carlo V, Cebollero Marcucci J, Beauchamp Roche F, Monasterio Hern·ndez J, DÌaz Troche JR, Su·rez Nieves AS, RamÌrez Ferrer LO: Prophilactic transduodenal sphincteroplasty for the prevention of retained common bile duct stones (In preparation).

6. Cotton PB, Geenen JE, Sherman S, Cunningham JT, Howell DA, Carr-Locke DL, Nickl NJ, Hawes RH, Lehman GA, Ferrari A, et al: Endoscopic sphincterotomy by experts is safe, even in younger patients with normal ducts. Ann Surg 1998; 227: 201-204.

7. Baker AR, Nepotolemeos JP, Leese T, Fossard DP: Choledochoduodenostomy, transduodenal sphincteroplasty and sphincterotomy for calculi of the common bile duct. Surg. Gynec Obstet 1987; 164: 245-251.

8. Miros M, Kerlin P, Srong R, Hartley L, Dikey D: Postcholedocoenterostomy îsump syndromeî. Aust NZ J Surg 1990; 60: 109-112.

9. Sivak M V Endoscopic management of bile duct stones. AM J Surg 1989;158 : 228-240

Estudios Originales:

The Abdominal Compartment Syndrome: A report of 3 cases including instance of endocrine induction

Victor M.Carlo, Gerhart Ramirez Schon, Giselle Suarez Irrizary, David Villareal Olivas, Juan Camps Barazoin, Angel Medina Torres
Ponce School of Medicine, Ponce, Puerto Rico

Summary: *Three patients with the abdominal compartment syndrome are presented and discussed. In one of the patients the condition was induced in an endocrine fashion, since trauma was sustained exclusively by the middle third of the left leg. The development of the syndrome as a remote effect of local trauma has never been reported previously. In all three instances only insignificant amounts of intraperitoneal fluid was found and the increase in abdominal pressure was due to severe edema of the messentery and retroperitoneum. Since the condition is highly lethal, early diagnosis is imperative, and this starts by carrying a high index of suspicion. Measurement of the intraperitoneal pressure easily confirms this diagnosis. It is emphasized that measurements at various sites, like bladder and stomach, in each patient is essential to confirm the diagnosis, since one of the sites may be rendered unreliable due to intraperitoneal processes impinging on the affected site and affecting its distensibility.*

INTRODUCTION:

A compartment syndrome is the series of untoward events that occur as a result of increasing pressure in a confined anatomical space. The increased pressure in fascial spaces of the extremities upon their reperfusion, is a well known example. When this syndrome occurs in the abdomen, Abdominal Compartment Syndrome (ACS), there occur critical systemic effects in addition to the local causes, that threaten the patients life. Increased intra-abdominal pressure, to the point of placing the patients life in jeopardy, has been the concern of surgeons who have had to repair abdominal defects where the intestine has lost its right to domicile, such as chronic large ventral hernias, diaphragmatic hernias and gastroschesis.

As far back as 1911, Emerson (1) studied the ill effects of increased pressure within the abdomen and found that intra-abdominal pressures of 27 to 45 cm. of water were lethal in experimental animals. However, it was not until 1984 that Rowlands (2) described the abdominal compartment syndrome and suggested the use of silos for temporary abdominal closure as the most appropriate surgical approach for decompression.

In the last few years a renewed interest in abdominal hypertension resulting in ACS has occurred (3, 4, 5, 6). The clinical definition of abdominal compartment syndrome addresses the increase in intra-abdominal pressure at the point where adverse, uncompensated hemodynamic changes occur that place the organism in danger of death, should they be sustained for any critical period of time. Examples where the syndrome may manifest include intra-abdominal bleeding , the use of packing in the control of bleeding , peritonitis, blunt abdominal trauma, free liquid or gas in the peritoneal cavity and, as evidenced by our three patients, post-traumatic massive edema and inflammation of the serosa and adjacent tissues.

ACS usually affects adversely the patients cardiovascular, pulmonary and renal functions. In the cardiovascular system there is a decreased venous return roduced by the compression of the inferior vena cava and retroperitoneal vessels. The inferior vena cava may be compressed at the diaphragmatic crura as the diaphragm is elevated (7). The increased pleural pressure diminishes atrial compliance, but atrial pressures remain normal or increase reflecting pleural pressure, in spite of the diminished return. There is a consequent drop in cardiac output, usually with a compensatory increase in peripheral resistance. The visceral blood flow is significantly diminished beyond that accounted for by the drop in cardiac output (8).

Respiratory mechanics are mainly affected by ACS when the increased intrabdominal pressure elevates the diaphragm, producing an important restrictive pulmonary lesion and increasing the pleural pressure. These events result in an increasing end inspiratory pressure to achieve a fixed tidal volume. In fact, increasing the inspiratory pressure by ventilator manipulation only aggravates the ACS (9) by increasing the adverse hemodynamic changes. Usually ventilatory insufficiency is the first manifestation of ACS, and oliguria always follows (10).

The renal manifestations of ACS are due to the venous, arterial and parenchymal compression produced by the intra-abdominal hypertension. Although the drop in cardiac output must have some

bearing; the renal impairment cannot be corrected by increasing the cardiac output to normal or supra-normal levels (11). The compression of the ureters that occurs with ACS is not the cause of the renal impairment, since stenting of the ureters does not correct the oliguria (11).

Other findings that may appear in ACS are increase in crerebrospinal fluid pressure and venous thrombosis (4, 12).

The most important step in the management of ACS is timely diagnosis, so physicians should include this entity in the differential diagnosis of patients with abdominal distention and respiratory problems. Confirmation entails measurement of the intra-abdominal pressure. This can be obtained in the clinical setting, by measuring the pressure within the stomach or urinary bladder that has been partially filled with 50 to 100 ml. of saline solution. In the case of the stomach, the fluid filled naso-gastric tube, whose tip is submersed within the gastric contents, can be used as a manometer and the baseline is taken at the mid-axillary line and the units of measurement are cm. of saline.

In the case of the urinary bladder, a central venous pressure apparatus is interposed at the urinary catheter arrangement and the baseline is taken at the pubic symphisis. Normal intra-abdominal pressure is atmospheric and patients with pressures up to 25 cm. of saline will usually not develop the syndrome with oliguria and respiratory impairment.

As pressures increase over 25 cm. of saline more patients require decompression and a pressure over 35 cm. of saline is an indication for decompression. It must be clear that the ACS is a clinical entity and cannot exist in the absence of respiratory impairment, however, the syndrome cannot exist without some decree of inta-abdominal hypertension.

Surgical decompression entails a celiotomy from xyphoid to symphsis pubis and usually the interposition of a membrane between the wound edges. This increases intra-abdominal space to accommodate its contents and reduce the intra-abdominal pressure to levels close to atmospheric . The membranes that have been used or improvised include an open genitourinary irrigation bag, an open 1000 ml. IV infusion bag, silastic membranes, absorbable mesh and Velcro-adjustable membranes. Primary closure may be effected if the ACS is due to surgical packing or blood (6,3,5).

CASE REPORTS:

Case Summary One: A 23 year old construction worker developed right lower quadrant abdominal pain, nausea vomiting and diarrhea four days prior to admission.

There was no concurrent illness and a family history revealed both parents to be diabetic. On physical examination an obese dehydrated male with generalized acute abdomen was found and the patient was resuscitated with intravenous saline solutions. At laparotomy a severe peritonitis with dilated bowel loops was found and the etiology was a perforated subserosal appendicitis with a large abscess extending from the right iliac fossa to the cul de sac.

About twelve hours postoperatively the patient had developed oliguria, presented tachycardia, the mean arterial pressure was 57 mm Hg and Hemoglobin was 19.3 Gm. %. Aggressive fluid replacement is instituted. The abdomen was tense and respiratory acidosis was found in spite of his having been kept on mechanical ventilation. The patient is sedated to improve ventilation. He is started on an intravenous inotropic agent.

On the first postoperative day the patient continues oliguric in spite of having increased his central venous pressure to 16 mm Hg and a Swan-Ganz catheter is inserted. The pulmonary wedge pressure was found to be 22 mm Hg and the rate of infusion of the inotropic agent was increased. This maneuver increased the mean arterial pressure by 10 mm Hg, decreased the pulmonary wedge presssure minimally to 19 mm Hg and kept the cardiac index, tachycardia and systemic vascular resistance about the same. The patient continued dehydrated and further hydration was continued. That evening the patient developed adult respiratory distress syndrome and septic shock is diagnosed. An observation as to the fluid sequestration in the abdomen was made. On the second postoperative day the intra-abdominal pressure was measured by instilling 50 ml. of saline into the bladder and the pressure was found to be 25cm. of saline. At 8:00 AM the patient had a cardiopulmonary arrest from which he could not be resuscitated.

Autopsy findings:
Septic shock secondary to perforated gangrenous appendicitis, intra-abdominal abscess and generalized peritonitis. The lungs showed hyaline membrane and acute pulmonary edema. There was hepato-splenomegaly with acute passive congestion and sepsis. The kidneys showed congestion and acute tubular congestion. There was no abnormality of the adrenal glands.

Case Summary Two: A 38 year old man with no history of systemic illnesses, but with history of heavy alcohol intake, sustained blunt trauma to his chest and abdomen with a steering wheel at 4:30 A.M., while driving without a seat belt. There was no history of loss of consciousness, he showed a closed fracture of his left femoral shaft and gross hematuria was noted on passing a urinary catheter in the emergency department.

On physical examination the patient had a pulse of 98 per min., tachypnea of 22 per min. and blood pressure 90/60. He was anxious, but well oriented in time, space and self. Multiple scattered superficial lacerations of his forehead due to the broken windshield glass impacts were noted. The patient presented a dry oral mucosa and the examination of his head and neck was unremarkable. He had contused areas over his right anterior chest, but showed good respiratory movements and clear lungs to auscultation. His abdomen presented epigastric tenderness but no signs of peritoneal irritation. The extremities showed the typical external rotation of his left foot due to the femoral shaft fracture and his neurological examination was negative.

In the emergency room blood gases were taken revealing a pH of 7.540, a pCO2 of 29.8 mm Hg, and a pO2 of 64 mm Hg, so an endotracheal intubation was performed and the patient assisted mechanically with an FIO2 of 40%, correcting the pO2 to 89 mm Hg. Chest Xray showed four fractured ribs on the right side and no hemo- or pneumo-thorax. The femoral fracture was immobilized with skin traction.

After one day of observation it was decided to perform an exploratory laparotomy on the patient on the basis of a decrease in 3 Gm. % of hemoglobin an increase in WBC count to 19,900, a silent abdomen with continued epigastric tenderness, although he had no signs of peritoneal irritation. At operation one liter of blood was found in the peritoneal cavity due to a grade IV laceration of the right lobe of the liver which was not bleeding at the time. There were no other significant findings.

On the first postoperative day the patient had a distended abdomen, ascribed to a paralytic ileus but he maintained a urine output of 100 ml. per hr., the hemoglobin remained stable and the arterial blood gases had corrected to very acceptable levels, prompting institution of the weaning process. However the serum creatinine level was at 1.9 mg. %. On the second and third postoperative days the patient continued with a good urine output and his serum creatinine reached normal levels of 1.3 and 0.4 mg. %. The blood gases remained well within the limits expected for an FIO2 of 40% and the chest X-ray remained with no change, so the process of weaning continued but the patient could not be disconnected from mechanical ventilation. The abdomen was described as distended and tense to palpation, there were no bowel sounds heard and copious drainage was obtained from the naso-gastric tube.

On the fourth postoperative day the patients blood pressure decreased to 90/50, he continued with a tachycardia of 133 per minute and developed a fever of 39.3 C. and his urine output decreased below 50 ml. per hour. A fluid challenge increased the urine output and increased the central venous pressure to 11 cm. of saline. The patients pO2 decreased to 80 mm. Hg with an unremarkable chest X-ray and the serum creatinine increased to 2.3 mg. %, and by that evening the tense abdominal distention became an obvious problem to be addressed. At this point the intra-abdominal pressure was measured with a CVP manometer, through a Foley catheter after instilling 100 ml. of saline in the bladder. The fluid overflowed the 35 cm. of saline mark. A Swan Ganz catheter was inserted and revealed a central venous pressure of 20mmHg and a pulmonary wedge pressure of 24mm. Hg. Subsequently the patient went into bradycardia and hypotension which did not yield to vigorous resucitation and died.

Autopsy findings:

The diagnostic summary is: 1) Abrasion of frontal region, 2) contusion of the anterior aspect of right hemithorax, 3) multiple rib fractures, 4) sternal fracture, 5) contusion right lung, 6) laceration of liver, 7) massive fatty degeneration of the liver, 8) peritonitis, 9) status post laparotomy, and 10) fracture left femur. The thorax was normal except for multiple rib fractures, a sternal fracture and several lung contusions with no other abnormalities that could have affected pulmonary mechanics under mechanical ventilation. The liver presents a laceration and marked yellowish discoloration. The peritoneal cavity contained 100 ml. of a reddish-brown fluid and the small and large bowel were distended appear dark and contain a moderate amount of dark fluid. The spleen revealed moderate congestion.

Case Summary Three: A 45 year old man was cutting a large branch from a tree and, upon dealing the last stroke, the branch cut loose ramming his left leg in its middle third. The man did not fall from the tree and was lowered to the ground by means of a utility ladder. There was no history of trauma at any other site of his body.

The past history revealed heavy drinking and smoking of one pack a day for 20 years. The review of systems did not add any information.

On physical examination he had a temperature of 36∞C., a pulse of 120 per min., respiration of 22 per min. and a blood pressure of 130/80 in a man that measured 71 inches in height and weighed only 135 pounds. The patient was anxious but alert and well oriented in time, place and self. The rest of the physical examination, including the abdomen and rectal exam, yielded no abnormalities other than that found in the left lower extremity. An open comminuted fracture of the tibia and fibula was noted in the left leg and multiple lacerations of the left thigh were found. The dorsalis pedis and posterior tibial pulses were present

and there was no sensory neurologic deficit. The motor aspect could not be examined because of pain.

Although the patient was admitted with a diagnostic impression of only an open tibio-fibular fracture and multiple lacerations left thigh, it was evident that he had sustained a significan blood loss from the injury. His Hemoglobin was found to be only 5.6 Gm.% on admission, with an hematocrit of 16.4 with normal prothrombin time but a partial thromboplastin time of 37.5 Vs. control of 29.1 and platelets of only 66,000. The physiologic effects of his blood loss were evidenced by arterial pH of only 7.165 and a pCO2 of 29.7 mm Hg, demonstrating a severe uncompensated metabolic acidosis. The Blood urea nitrogen and serum creatinine were within normal limits. The patient was transfused with packed cells and challenged with normal saline solution. After correction of his anemia and acidosis, he was transfered to the Operating Room where cleansing and debridement , open reduction with external fixation and hemostasis was performed. The procedure was well tolerated and his endotracheal tube was removed postoperatively since he did not require ventilatory support.

Two hours after the operation he started to have difficulty breathing, his abdomen suddenly distended and the urinary output abruptly halted. In spite of the marked abdominal distention the patient experienced no pain. A diagnostic peritoneal lavage was performed that was grossly negative. The peripheral pulses in the lower extremities, which were present on admission, disappeared. The blood pressure dropped to 40/0 and endotracheal intubation, aggressive fluid resuscitation with crystaloids and intravenous inotropic agents were instituted. Since response to these measures was meager, the patient was transferred to the operating room.

Upon performing the celiotomy the bowels burst out of the abdomen, the gut was found to be very pale, but not cyanotic and the mesentery and the retoperitoneum was massively edematous. After a short period of observation the gut recovered its color. There was no finding that could be attributed to trauma, however, the liver demonstrated the nodular surface of Lannecs cirrhosis. The spleen was normal there were no peritoneal lacerations what so ever. The abdomen was closed by suturing an opened Intravenous fluid bag to the fascia, maintaining with this maneuver an intra-abdominal pressure within reasonable limits. With this tratment the blood pressure stabilized and the peripheral pulses were readily palpated. Postoperatively the patient developed a profuse diuresis of over 500 ml. per hour. By the following day the arterial blood gases revealed no abnormality and the measured intrabdominal pressure was only 10 cm. of saline. Hemostasis of the wound had permitted transfusing the patient up to a hemoglobin of 12.1 Gm.% but his platelet count remained low at 20,000. Prothrombin and partial thromboplastin times were near control levels. By the sixth postoperative day the patients platelet count had raised to 300,000, so his abdomen was explored again and the temporary intravenous fluid bag closure was changed to a conventional closure. The patient followed a benign postoperative course and his prolonged hospital stay was due to repeated interventions for his open fracture.

DISCUSSION

Patient number one presented a severe purulent peritonitis due to a neglected perforated appendicitis. Soon after surgery he was hypotensive and all efforts to correct his fluid deficit were unsuccessful, as evidenced by a sustained hemoglobin of 19.3 Gm. % and oliguria. The resuscitation fluids were being sequestered in a third space in the mesentery, retroperitoneum and intra-abdominal organs, since only 100 ml. of intraperitoneal fluid was found at autopsy. All abdominal organs were described as congested except for the adrenals. This is consistent with ACS. It has been documented that the ischemia suffered by all the abdominal organs in the ACS is spared in the adrenal gland. The reason for this state of ischemic immunity of the adrenal gland in ACS is not known. An intra-abdominal pressure of 25 cm. of water in the face of pulmonary and renal impairment is enough to diagnose ACS, however, the diagnosis becomes certain with the renal involvement, the difficulty in ventilation and a tense abdomen accompanied by increased central venous pressure and pulmonary wedge pressure, in spite of concomitant evidence of dehydration.

The patient was running mean arterial pressures in the fifties; the highest recorded was 67 mm Hg, and an intra-abdominal pressure of 25 cm H2O lowers the perfusion pressure sufficiently to implicate this as an important factor in the hypoperfusion of the abdominal viscera. Since the patients venous pressure was 25 cm. H2O, the role of the intra-abdominal pressure on the development of congestion of abdominal organs becomes obvious. The ACS may occur in the face of septic syndrome with multiple organ failure. Since manifestations of both these syndromes are similar by different mechanisms, and may coexist, potentiating each other, objective diagnosis of ACS is essential to institute its treatment. In this particular patient, a surgical decompression would have permitted the treatment of multiple organ failure without extraneous factors complicating the therapeutic setting, however, the prognosis of such massive sepsis was very poor.

In patients one and two, the intra-abdominal pressure was measured within the bladder. The first

had only 50 ml. of saline instilled with a preassure measurement of 25 cm. of saline and the second had 100 ml. inserted with a pressure measurement of over 35 cm. of saline. For more accurate results 100 ml. of fluid should be within the bladder, allowing us to speculate whether the pressure would have been higher in patient one, should the accepted amount have been used.

Another important point we have learned in using this technique is illustrated by a patient with colonic, gastric and hepatic lacerations from a bullet wound, treated by primary repair of the stomach and limited colonic resection at the perforation site with construction of a double barrel colostomy just anterior to the bullet exit site at the left upper abdomen. This patient turned out not to have an ACS in spite of having severe abdominal distention, respiratory insufficiency and renal impairment. The severity of the latter two manifestations required prolonged mechanical ventilation and two sessions of hemodialysis for their resolution, but definite disappearance of the organ failure did not occur until 2,600 ml. of pus were drained from the abdomen and an enterocutaneous fistula was established, supporting the diagnosis of multiple organ failure due to sepsis. During the period of severe abdominal distention pressures were measured in the bladder, at the colostomy and at the stomach. The pressure at the bladder was 37 cm. of saline, at the colostomy it was 29 cm. of saline and at the stomach it was 18 cm. of saline. Five days later, just before the drainage of the intra-abdominal abscesses, the pressures were recorded as being 38 cm. of saline at the bladder, 25 cm. of saline at the colostomy and 20 cm. of saline at the stomach site. At laparotomy walled off abscesses were found at the bladder and left peritoneal gutter and these inflammatory processes impinged on the bladder and the colostomy making the measurement of pressures at these sites unreliable. We therefore recommend measuring intra-abdominal pressures at different sites and accepting the lowest of these pressures as the accurate reflection of the pressure within the peritoneal cavity.

It is also interesting to observe that patients two and three with ACS had liver impairment. An association between ACS and liver disease has been described, however, neither of these patients developed ascites, the factor incriminated for this association. The mechanisms for this association should not be explained on purely mechanical considerations, such as the accumulation of ascites, and local hemodynamic and inflammatory responses should be investigated. Our third patient should give a clue to the mechanism, since there was no abdominal trauma and only isolated bone and soft tissue trauma to the leg causing profuse bleeding and metabolic acidosis with decrease in platelet count. Much of this manifestation can be explained by the same mechanism of hepatic damage during shock by variceal hemorrhage, where there is sluggish flow within the engorged hepatic sinusoid triggering local intravascular coagulation and consequent further increase in portal pressure. This, however, does not explain the massive mesenteric and retroperitoneal edema, that seems to have been the consequence of endocrine inflammatory stimuli by cytokines liberated at the wound site to an end organ that has been sensitized by the pre-existing liver impairment and its response to the pathological hemodynamic setting.

Lastly it is interesting to observe that pathologists fail to diagnose this syndrome. This is a clinical syndrome that does not manifest particular anatomical clues for pathological diagnosis.

REFERENCES:

1. Emerson H: Intrabdominal pressures. Arch Int Med 1911; 7: 754-794.
2. Rolands B, Jand Flynn TC: Temporary wound closure with a silastic chimney. Contemp Surg 1984; 24: 120.
3. Schein M, Wittman DH, Aprahamian C, Condon RE: The abdominal compartment syndrome: Clinical consequences of elevated intra-abdominal pressure. J Am Coll Surg 1995; 180: 745-751.
4. MacDonnel SP, Lalude AS, Davidson AC: Letters to the Editor, J Am Coll Surg 1996; 183:
5. Mayberry JC, Mullins RA, Trunkey D: Prevention of abdominal compartment syndrome by absorbable mesh prosthesis closure. Arch Surg 1997 Sept.; 132(9): 957-961.
6. Burch JM, Moore EE, Amoore F, Franciose R: The abdominal compartment syndrome. Surg Clin NA 1997; 76(4): 833-842
7. Doppul RV, Dimson RM, Rockoff: Mechanisms of obstruction of the infradiaphragmatic portion of the vena cava in the presence of increased intra-abdominal pressure. Invest Radiology 1966; 1: 37-53.
8. Caldwell CB, Ricotta JV: Changes in visceral blood flow in the elevated intra-bdominal pressure. J Surg Res 1987; 43: 14-20.
9. Richardson JD, Trinkle JK: Hemodynamics and respiratory alterations with increased intra-abdominal pressure. J Surg Res 1976; 20: 401-404.
10. Eddy et al Abdominal Compartment Syndrome: The Nashville Experience. Surg Clin NA 1997; 77: 4. 801-812
11. Shenaski JH, Gillenwater JY: The renal hemodynamic and functional effects of external counter pressure. Surg Gynecol Obstet 1972; 134: 253-258.
12. Ivatury RR, Diebel L, Porter JM, Simon RJ: Intra-abdominal hypertension nd the abdominal compartment syndrome. Surg Clin NA 1977; 77(4): 873-880

Vol. 90 • 7-8-9-10-11-12 / 1998 • Pág. 126, 129

Estudios Originales:

The Anatomic Distribution of Colorectal Cancer in a New York City Puerto Rican Group

Deowall Chattar-Cora, MD[1], Godfrey D. Onime, MD[2], Iren S. Valentine, MS[1], Libertad Rivera-Cora[1]

Abstract: *Studies have attempted to define the anatomic distribution of colorectal cancer in some black and white groups of the U.S. However, little, if any research has looked at the regional distribution of colorectal cancer in an American Hispanic, especially Puerto Rican, group. This study attempts to provide some insight into the subsegmental distribution of colorectal cancer in this group of the American population which has a heavy concentration of people in many major U.S. cities.*

We retrospectively reviewed the charts of Puerto Rican patients who had colorectal adenocarcinoma and were on the files of the tumor registries of two principal teaching hospitals of a New York City medical school from 1976-95, and collected the age and location of the cancers. Patients were self identified as being of Puerto Rican descent. Right colon cancers were from the cecum up to the hepatic flexure, left from the splenic flexure down to the sigmoid colon, rectal which included rectosigmoid, transverse and cancers of unknown locations. The latter were not included in the anatomic analysis since the location was not known. There were eleven of these patients. The anatomic analysis was of 134 patients. There were 67 women, and 78 men with a mean age of 60.3 years, and 63.7 years respectively with an overall mean age of 62.2 years. The anatomic distribution of the cancers were as follows: right colon cancer represented 22.4% or 30/134, transverse lesions equaled 1.5% or 2/134, left cancers were found in 38.0% or 51/134, rectal malignancies equaled 38.0% or 51/134.

Previously, it has been shown that the presentation of right sided colorectal cancer in white and black Americans is greater than the 22.4% seen in the Puerto Rican group of this study. However, these previous groups have been found to have 50% of cancers located distal to the splenic flexure, similar to the Puerto Ricans in this study. The average age of Puerto Ricans presenting with colorectal cancer compared to the average age of the general population may be different. Screening techniques for colorectal cancer may be adequate for detecting colorectal cancer in Puerto Ricans, however if they are indeed presenting at a relatively early age, the techniques may need to be applied earlier in comparison to the general American population. Further study is needed to see if the age of presentation is indeed as early as suggested by the present study.

Introduction

Malignant neoplasms of the colorectum have been studied extensively and they represent a very common potentially fatal gastrointestinal disease encountered in clinical practice. It is estimated that more than 130,000 people will be diagnosed with colorectal cancer, and 55,000 will die of the disease each year.[1] At present colorectal cancer is the third leading cause of cancer death for all citizens of the United States.[1] For Hispanic Americans on the island of Puerto Rico it is also the third leading cause of neoplastic death.[2] This is unfortunate given the fact that with appropriate screening and detection many of these cases can be diagnosed and treated early, minimizing the morbidity and mortality associated with this disease.

Colorectal cancer is a disease that can be easily managed if diagnosed early with proper screening. In an effort to decrease the morbidity and mortality associated with this disease studies have been performed to gain insight into the anatomic distribution[3-5], average age of presentation with the disease[6-8], and mean age of presentation for the different regions of the colon.[9,10]

Several studies have been done defining the anatomical distribution of colorectal cancer in black and white American groups.[4,5] It has been shown that black Americans have a high incidence of right sided

[1]*Department of Surgery Morristown Memorial Hospital Morristown, NJ*
[2]*Department of Medicine Columbia University College of Physicians and Surgeons New York, NY*
Address Reprint Requests to: Deowall Chattar-Cora, MD
100 Franklin St. Building H110
Morristown, NJ 07960 973-267-8556
email: Deowallchattar@yahoo.com

lesions[4,5], while both blacks and whites have a large proportion of their lesions distal to the splenic flexure of the colon. Other literature has suggested that the average age of presentation of colorectal cancer in the American population is 72 years.[11] Unfortunately Hispanics, especially Puerto Ricans have been under represented in these studies. Thus little is known about the clinical profile of this disease in Puerto Rican Americans even though in many urban cities like Chicago[12], Miami[13], and New York City[14] they represent a large percentage of the population.

The few studies that have looked at colorectal cancer in Hispanics addressed the relative risk, incidence and/or mortality of cancer in this group, and compared them to the white non-Hispanic groups of the U.S.[15-23] Hispanics were consistently found to have a lower mortality and incidence of disease. However, we were unable to find any lite-rature that specifically addressed the segmental distribution, and age at presentation of colorectal cancer in the Puerto Rican segment of the American population.

In this present study we analyze the regional distribution of colorectal cancer in a New York City Puerto Rican group, age of presentation for colorectal cancer and analyze the ages at which the patients present with cancer in each anatomic location.

The information obtained from this type of analysis may prove helpful in developing guidelines for screening and work-up of patients of this ethnic group. In the current environment of managed care, cost plays a significant role in the allocation of health care resources. Groups of patients whose health care data is incomplete or underrepresented may be denied access to vital resources.

Materials and Methods

Patients who were in the files of the tumor registries of two New York City hospitals affiliated with New York University School of Medicine were identified. The medical records of 113 patients who presented to hospital A between 1976-1995, and 32 patients who presented to hospital B between 1984-1994 were retrospectively reviewed. Patients from hospital B were include in order to get a more accurate reflection of the parameters examined in this study. Only patients who were born in Puerto Rico, or identified themselves as being of Puerto Rican descent, and had an invasive procedure performed (surgery or endoscopy) with a pathologically confirmed diagnosis of adenocarcinoma of the colon and/or rectum were included in this study. Patients who had suspected colorectal cancer and presented to hospital B before 1984 were not included because we were unable to confirm the pathological diagnosis. Furthermore, patients who presented to this same medical center after 1994 were not included because all of the needed data were not available at the time the information was collected.

The anatomic location of the tumors were classified as being right (extending from the cecum up to the hepatic flexure), transverse, left (from the splenic flexure to the sigmoid colon), or rectal. If the lesions were classified as being sigmoid, they were only included in the left category, while lesions defined as recto-sigmoid cancers were only classified as rectal cancers. Patients who had metastatic colorectal cancer or, if the pathology report stated "not otherwise specified" attempts were made to identify the location by reading the surgical or endoscopic report, and information in the chart. If unsuccessful these cases were classified as colon CA as similarly done by others.[24] These cases were not included in the anatomic analysis. Appendicial and anal cancers were excluded from the study due to possible histological[25-27] and etiological differences.[26-28]

Results

The breakdown of patients with the pathological diagnosis of colorectal cancer at hospital A during the period studied was 46 men and 67 women. All 32 patients from hospital B were men. The overall male to female ratio for the combined hospitals was 54.1% to 45.9%. When hospital B's group was excluded, the male to female ratio changed to 40.7% to 59.3%.

All of the patients had a mean age of 62.2 years, with men having an average age of 63.7 years, and women having a mean age of 60.3 years.

The anatomic location of the cancers were as follows: right colon represented 22.4% (30/134), transverse equaled 1.5% (2/134), left colon, including sigmoid colon was found to represent 38.0% (51/134), and rectal cancer equaled 38.0% (51/134).

The average ages for the different anatomic locations are as follows. In patients with right colon cancer it was 63.4 years, transverse 67.0 years, left colon 61.6 years, in rectal cancer it was 61.2 years, and in colon cancer without known location it was 69.8 years.

Discussion and Conclusions

Historically, minorities especially Hispanics have been under represented as the subjects of clinical investigation and in the development of screening recommendations. The goal of the present study was to provide some insight into the clinical profile (ie anatomic distribution, and age of presentation) of colorectal cancer in a Puerto Rican group residing in an urban environment.

At present the American Cancer Society's screening recommendations for colorectal cancer in an asymptomatic patient is a digital rectal examination beginning at age 40, and starting at age 50 annual fecal occult blood test, and sigmoidoscopy or colonoscopy every five years, or double contrast barium enema every 5-10 years.[1]

Anatomic Distribution

As demonstrated previously in other groups, we found that our Hispanic group had a similar regional distribution of colorectal cancer with more than 50% of cancers in the distal colon and rectum.[8,29,30] Because many of these lesions are distal to the splenic flexure, flexible sigmoidoscopy may prove beneficial in detecting these lesions and may serve as a screening tool in Puerto Rican patients at high risk for colorectal cancer. Our low numbers of transverse lesions may be secondary to our inclusion of hepatic and splenic flexure lesions with right and left colon cancer respectively.

Age of Presentation

Overall the patients in the present study are relatively young with the mean age of our patients being 62.2 years. In comparison to other groups in North America, our Hispanic group is relatively young.[6-8] However our patients are similar to the average age of the subjects in a study by De Llano Rodriguez et al.[31] The latter studied a group in Spain that has historic genetic ties to Puerto Rico. The relatively young age of our patients, and the historic ties with Spain's population raises the possibility of genetic predisposition for early presentation of colorectal cancer in New York City Puerto Ricans. Unfortunately we did not compile any family history which may provide some insight into the role of genetic descent in the development of colorectal cancer in our group of patients. We do not believe that socioeconomic factors are at play here. In a previous study of a multiethnic group which compared the age of presentation for colorectal cancer in patients of the same socioeconomic background, it was found that Caucasians presented at significantly older age than Hispanics.[32] Ultimately, the cause for the early presentation may prove to be multifactorial.

Since the key to successful treatment is screening and early detection, the precise factors involved in cancer development in Puerto Rican patients are crucial to identify. If our finding that this ethnic group is presenting at an early age with colorectal cancer, the current screening recommendations for this disease may require adjustments when looking for this malignancy in Puerto Ricans.

Comparison of the mean ages of presentation for the different anatomic locations reveals an increase from distal to proximal colon, 61.2 years for rectal cancer and 63.4 years for right sided cancer. Although not significant this is consistent with the findings of others who found similar results in their groups, i.e. patients who had proximal cancers were more likely to be older.[9,33,34] This is likely due to the fact that right sided cancers have a tendency of being asymptomatic[35], and are more likely to present with occult bleeding.[35-37] These patients are apt to seek medical attention when they have symptoms consistent with obstruction or perforation.[35,36] Left sided lesions on the other hand have a greater tendency of presenting with lower abdominal pain[35], hematochizia[37], and changes in bowel habits.[37] Thus these patients are more likely to recognize a change in their health, and seek care at an earlier period in their life. These factors are the presumed reason that patients who have right sided lesions are more likely to present with more advanced stages and worse prognosis of colorectal cancer than patients with left sided disease.[38]

Colorectal Cancer Screening Recommendations and Puerto Ricans

If it takes 2-10 years for a malignant process to become clinically detectable[39,40], and we start screening Puerto Rican patients every five years with sigmoidoscopy starting at age 50 we may miss some cancers in this segment of the American population if many Puerto Ricans are found to be young when they develop colorectal cancer.

The findings of this study may be unique to the centers examined in this study, or may be an accurate reflection of the clinical picture of this disease in this segment of the American population. Further study is warranted to determine if this profile of colorectal cancer is an accurate reflection of the disease presentation in Puerto Ricans so that appropriate screening programs can be implemented if indicated.

Citations

1. American Cancer Society. *Cancer Facts & Figures-1997*. Atlanta; 1997. American Cancer Society.
2. Registro Central de Cancer. *Cancer en Puerto Rico 1991*. San Juan 1993. Departamento de Salud de Puerto Rico.
3. Nomura AM, Kolonel LN, Hinds MW. Trends in the anatomical distribution of Colorectal carcinoma in Hawaii, 1960-78. *Dig Dis & Sci* 1981; 16:1116-1120.
4. Johnson Jr H, Carstens R. Anatomical distribution of colonic carcinomas: interracial differences in a community hospital population. *Cancer* 1996; 58:997-1000.
5. Thomas Jr Cr, Jarsoz R, Evans N. Racial differences in the anatomical distribution of colon cancer. *Arch Surg* 1992; 127:1241-1245.
6. Kashtan H, Papa MZ, Stern HS. Is age an inde-pendent variable in the morbidity and mortality of patients with colorectal cancer? A prospective study. *Can J Surg* 1991; 34:374-376.
7. Lichtman SM, Mandel F, Hoexter B, Goldman IS, Budman DR, Labow S, Moseson M, Stiel L, McKinley

M. Prospective analysis of colorectal carcinoma. Determination of age-site and stage relationship and the correlation of DNA index with clinicopathologic parameters. *Dis Col & Rect* 1994; 37:1286-1290.

8. Taylor RH, Moffet FJ. Profile of colorectal cancer at a community hospital with a multiethnic population. *Am J Surg* 1994; 167:509-512.
9. Fleshner P, Slater G, Aufses AH. Age and sex distribution of patients with colorectal cancer. *Dis Col Rect* 1989; 32:107-111.
10. Slater G, Papatestas AE, Tartter PI, Mulvihill M, Aufses AH. Age distribution of right and left-sided colorectal cancers. *Am J Gastroenterology* 1982; 77:63-66.
11. Smart CS. Screening and early diagnosis. *Cancer* 1992; 70:1246-1251.
12. United States Department of Commerce, Bureau of the Census. The population of Chicago, CB-91-51. United States Department of Commerce, Bureau of the Census Washington DC, 1991.
13. United States Department of Commerce, Bureau of the Census. The population of Miami, CB-91-75. United States Department of Commerce, Bureau of the Census Washington DC, 1991.
14. United States Department of Commerce, Bureau of the Census. The population of New York City, CB-91-68. United States Department of Commerce, Bureau of the Census Washington DC, 1991.
15. Mallin K, Anderson K. Cancer mortality in Illinois Mexican and Puerto Rican immigrants, 1979-84. *Int J Can* 1988; 41:670-676.
16. Rosenwaike I, Shai D. Trends in cancer mortality among Puerto Rican-born migrants to New York City. *Int J Epi* 1986; 14:30-35.
17. Warshauer ME, Silverman DT, Schottenfeld D, Pollack ES. Stomach and colorectal cancers in Puerto Rican-born residents of New York City. *J Natl Can Inst* 1986; 76:591-595.
18. Wolfgang PE, Semeiks P, Burnett WS. Cancer incidence in New York city Hispanics, 1982-85. *Ethnicity and Dis* 1991; 1:263-272.
19. Davis FG, Persky VW, Ferre CD, Howe HL, Barrett RE, Haenszel WM. Cancer incidence of Hispanics and non-Hispanic whites in Cook County, Illinois. *Cancer* 1995; 75:2939-2945.
20. Trapido EJ, Burciaga-Valdez R, Obeso JL, Strickman-Stein N, Rotger A, Perez-Stable EJ. Epidimeology of cancer among Hispanics in the United States. *Monographs Natl Can Inst* 1995; 18:17-28.
21. Rosenwaike I. Cancer mortality among Mexican immigrants in the United States. *Publ Hlth Rep* 1988; 103:195-201.
22. Martin J, Suarez L. Cancer mortality among Mexican Americans and other whites in Texas, 1969-80. *Am J Publ Hlth* 1987; 77:851-853.
23. Menck HR, Henderson BE, Pike MC, Mack T, Martin SP, SooHoo J. Cancer incidence in the Mexican-American. *J Nat Can Inst* 1975; 55:531-536.
24. Stewart RJ, Robson RA, Stewart AW, Stewart JM, Macbeth WA. Cancer of the large bowel in a defined population: Cantebury, New Zeland 1970-4. *Brit J Surg* 1979; 66:309-314.
25. Hauser H, Wolf G, Uranus S, Klimpfinger M. Neuroendocrine tumors in various organ systems in a ten year period. *Europ J Surg Oncol* 1995; 21:297-300.
26. Pollastri E, Brosutti O, Montenovo A, Bergeo A, Moroni J. Adenocarcinoma of anal canal. Report of a case and review of the literature. *Acta Gastroenterologia Latinoamericana* 1994; 24:239-244.
27. Tarazi R, Nelson RL. Anal adenocarcinoma: a comprehensive review. *Sem in Surg Oncol* 1994: 10:235-240.
28. Daling JR, Weiss NS, Klopfenstein LL, Cochran LE, Chow WH, Daifuku R. Correlates of homosexual behavior and the incidence of anal cancer. *JAMA* 1982; 1988-1990.
29. Devessa SS, Chow WH. Variation in colorectal cancer incidence in the United States by sub-site origin. *Cancer* 1993; 71:3819-3826.
30. Winawer SF, Schottenfeld D, Flehinger BJ. Review of colorectal cancer screening. *J Nat Can Inst* 1991; 243-253.
31. De Llano-Rodriguez I, Rodrigo-Saez L, Prados-Cano D, Schleiman-Helabi H. Epidemiology of cancer of colon and the rectum in the Asturias (1977-1981). *Revista Española de las Enfermedades del Aparato Digestivo* 1989; 76:660-668.
32. Cooper GS, Yuan Z, Ladefeld CS, Johanson JF, Rimm AA. A national population based study of incidence of colorectal cancer and age. Implications for screening in older Americans. *Cancer* 1995; 75:775-781.
33. Chattar-Cora D, Onime GD, Altman G. Colorectal cancer in a multiethnic innercity urban group: its anatomical and age profile. Abstract 2364 presented at the 99th annual meeting of the American Gastroenterological Association. New Orleans, LA 1998.
34. Kemppainen M, Raiha I, Rajala T, Sourander L. Characteristics of colorectal cancer in elderly patients. *Gerontology* 1993; 39:222-227.
35. MacKeigan JM, Senagore AJ. Colorectal cancer: general considerations. In: Mazier WP, Levein DH, Luchtefeld MA, Senagore AJ, eds. Surgery of the colon, rectum and anus. Philadelphia WB Saunders 1995.
36. Kodner IJ, Fry RD, Fleshman JW, Birnbaum EH. Colon, rectum and anus. In: Schwartz SI, Shires GT, Spencer FC, eds. Principles of Surgery. New York McGraw Hill 1994.
37. Diaz-Plascencia J, Tantalean E, Urtecho F. Colorectal cancer: its clinical picture and survival. *Revista de gastroenterologia del Peru* 1996; 16:48-56.
38. Cahpius PH, Newland RC, Macpherson JG, Dent O, Payne JE, Pheils MT. The distribution of colorectal carcinoma and the relationship of tumor site to the survival of patients following resection. *Aust New Zeland J Surg* 1981; 51:127-131.
39. Lance P, Grossman S, Marshall J. Screening for colorectal cancer. In: Gastrointestinal cancers: biology, diagnosis and therapy. Rustgi AK ed. Baltimore Lippincott-Raven 1995.

Vol. 90 • 7-8-9-10-11-12 / 1998 • Pág. 130, 133

Estudios Originales:

Primary Cardiac Myofibroblastic Sarcoma, Case Report and Review of Diagnosis and Treatment of Cardiac Tumors

Gursharan Dhillon, M.D.; Edwin Rodríguez-Cruz, M.D.***
*Mustafa Kathawala, M.D.***; Nasser Alqassem, M.D.*****

Abstract: *Primary cardiac tumors are rare entities with a frequency between 0.0017% to 0.28%. We report a 53 year old male with a primary cardiac myofibroblastic sarcoma that presented with a hemorrhagic pericardial effusion. A review of the literature is presented with a brief discussion of the clinical presentation diagnosis and treatment of benign and malignant primary cardiac tumors.*

Introduction

Boneti, in 1700, is credited with the first description of a primary cardiac tumor, but many believe the description by Albers, in 1835, to be the first authentic report. (1, 2) Although primary tumors of the heart have been recognized for centuries, it was not until 1934 when an antemortem diagnosis was made. (3) In 1952. angiography was used for the diagnosis (4), but it was not until 1955 when the first successful removal of an intracardiac tumor was performed. (5) Primary cardiac tumors are rare, with a frequency between 0.0017% and 0.28% based on autopsies. (6, 7) About 75% of them are benign and 25% are malignant. (6-9) This frequency has not changed over the last decade. Secondary tumors (metastasis) of the heart are 10 to 40 times more frequent. (9) Lam, et al., (10) reviewed 12,485 autopsies and they found only 7 cases of primary neoplasm of the heart versus 154 cases of secondary heart tumors.

Case Presentation

53 year old caucasian male who complained of night sweats for 2 months and progressive shortness of breath associated with right sided chest pain for 1 month. The review of systems revealed increased generalized fatigue and weakness of weeks duration. He used to smoke 2 packs per day for 30 years but quit 10 years prior to this admission. He only took aspirin or acetaminophen for pain. He had a brother on chemotherapy for colon cancer at the time of admission.

On physical examination the patient was afebrile, pulse was 100 bpm, RR 18, pulse oxymetry 92% on room air, BP= 140/95 mmHg. His cardiovascular exam was essentially normal except for distant heart sounds. He had bilateral basilar crackles in the lungs and hepatomegaly. An echocardiogram showed a large pericardial effusion with early signs of tamponade. The fluid was drained by a pericardial window. It was grossly bloody and suggestive of an exudate, showing no organisms. A pericardial biopsy revealed acute and chronic inflammation. No malignant cells were found in either one of them.

His shortness of breath did not improve and on the 3rd day of admission a ventilation/perfusion scan demonstrated multiple segmental defects suggestive of pulmonary embolism. An ultrasound of the lower extremities was positive for deep venous thrombosis. Heparin was started and by the 5th day of admission he had some improvement in his respiration but he remained tachycardiac and febrile. A repeat transthoracic echocardiogram was suggestive of a mass in the left atrium. A transesophageal echocardiogram and chest CT scan were performed. An open heart biopsy was carried out. The tumor was felt to be unresectable. The final pathology report was that of a primary cardiac myofibroblastic sarcoma of the left atrium with extension to the pulmonary veins.

**Resident Department of Combined Internal Medicine/ Pediatrics Saint Joseph Mercy Oakland- Pontiac, Michigan*
*** Fellow Cardiology Children's Hospital of Michigan,Wayne State University- Detroit, Michigan*
****Chief Resident Department of Internal Medicine Saint Joseph Mercy Oakland*
*****Chief Resident Department of Internal Medicine Saint Joseph Mercy Oakland- Pontiac, Michigan*
Address for reprints: Edwin Rodríguez-Cruz, M.D. Work: Division of Cardiology, Children's Hospital of Michigan 3901 Beaubien Blvd. Detroit, Michigan 48201-2196
Tel: (313) 745-5484 (secretary) Beeper: (313) 745-5111 #7917 E-Mail: ERODRI@pol. net

Discussion

Benign Tumors

Of the benign tumors, myxomas are the most commonly diagnosed. They account for 50% of all cardiac tumors for which surgical resection is often curative. (11, 12) When localized in the left atrium, they are known to embolize and metastasize.(12)

Other types of benign tumors include (6-11) rhabdomyomas, especially in children and in association with tuberous sclerosis; (ii) lipomas, solitary or in clusters found equally in males and females; (iii) fibromas, predominantly in children; (iv) teratomas; (v) angiomas, which may occur in any part of the heart and tend to form blood vessels (hemangioma), or lymph vessels (lymphangioma). Other benign cardiac tumors include (13): fibroelastomas, benign cystic tumors, leiomyomas and fibroelastic papillomas. The frequency of appearance depending on the studied population. Although benign, they can have more aggressive clinical course than even a malignant tumor of the heart depending on their location. (13)

The mesotheliomas are common primary tumors of the pericardium. Although benign tumors, some consider them quite dangerous because they have the propensity to produce atrioventricular conduction disturbances and sudden death due to their preferred intramyocardial localization. (8)

Malignant tumors

Loeffler and Grille (14) concluded that angiosarcoma is the most common malignant tumor, 3 1%, followed by rhabdomyosarcoma, 21%, fibrosarcoma, 11%, and lymphoma, 6%; with other tumors accounting for 16%. Other primary malignant tumors of the heart include: choriocarcinoma (15), leiomyosarcoma (16), histiocytoma (16), liposarcoma (16, 17), and osteogenic sarcoma (1, 2, 16), among others.

Myofibroblastic sarcomas (18, 19) are poorly delineated sarcomas which consists of spindle celís. They stain positive for vimentin, desmin and/or actin. The presence of abundant rough endoplasmic reticulum, fibronexus junctions and fibronectin fibrils are characteristic of them. However, pleomorphism is not uncommon. They arise from the soft tissue, and should be differentiated from other neoplasms (i.e. myxosarcomas, rhabdomyosarcomas, leiomyosarcomas) with similar features. To our knowledge there are only two previous reports of myofibroblastic sarcoma in the heart, (20, 21) although today this term is used by some experts to refer to fibrosarcomas.

Diagnosis

The diagnosis of any intra or extracardiac mass is a challenge for any physician. Cardiac neoplasm are known to present with non-specific findings. (7-9, 16) However, in the last 2 decades, advances and improvements in diagnostic tests and techniques have made a marked impact on the diagnosis of cardiac neoplasms.

The diagnostic evaluation should be done in a schematic fashion. An electrocardiogram, echocardiogram, chest roentgenogram, and CT scan or MRI should be part of every evaluation. Two-dimensional echocardiogram as well as the transesophageal echocardiogram achieve the highest sensitivity in detecting a mass. (9, 17, 22, 23) The transthoracic echocardiogram is the most important of the non-invasive procedures. (9) Transesophageal echocardiogram is useful in evaluating the superior portion of the right atrium and paracardiac areas. (17, 22) Although CT scan or MRI are mostly used to obtain more information about the neoplasm (i.e. metastasis), they are powerful tools for the establishment of the diagnosis. (9, 23)

The invasive procedures have diminished in popularity due to improvement of the non-invasive procedures. A cardiac catheterization and pulmonary angiogram, however, can give important and necessary information before surgery. Radionuclide methods may add information regarding the extent of invasion of the neoplasm. (9) Hausheer, et al., (24) emphasized the importance of endomyocardial biopsy because it can be conclusive rather than suggestive of a diagnosis. They compared the risks of endomyocardial biopsy versus cardiac catheterization and versus thoracotomy, and found it was the same in the former and less in the latter comparison, respectively. In contrast, Rettmar, et al (13) states that it could be false negative in up to 50% of cases. Pericardiocentesis as well could be of limited value for the diagnosis of intracavitary tumors when they present with pericardial effusion. (25-27)

Pericardial effusion

Although bloody pericardial effusion is not an uncommon presentation for a primary or secondary cardiac malignancy, its presence is less ominous than hemorrhagic pleural or peritoneal effusions.(28) The etiology is variable and includes: infection, trauma, collagen vascular diseases, pulmonary embolism, radiation therapy, myocardial infarction, (28) congenital heart disease (29), hemoglobinopathies (30), or it could be simply idiopathic. (28) The clinical presentation could range from asymptomatic to acute tamponade.

The evaluation of a bloody fluid is of extreme importance. The pH, pCO2 and pO2 are useful in the determination of the source of the effusion when compared to venous blood tests. (31) Cytology by itself could give false negatives. (25-27) Today, carcinoembryonic antigen (CEA) can be performed as an adjuvant for the recognition of malignant effusions. (32)

The treatment of a clinically significant malignant pericardial effusion is drainage by percutaneous or surgical approach. The consideration of the instillation of chemotherapy in the pericardial sac is also important, especially for recurrent cases. (33,34)

Differential diagnosis of cardiac tumors

The differential diagnosis of cardiac tumors is broad because they can imitate other cardiovascular diseases and their signs and symptoms are shared by other conditions. These include: pericarditis, coronary artery disease, dilated cardiomyopathy, congestive heart failure, pulmonary hypertension, pulmonary embolism, restrictive cardiomyopathy, valvular disease, endocarditis, metastasis to the heart autoimmune diseases, and primary cardiac disease causing cardiac arrhythmias. (2,6, 7, 9-13)

Treatment and complications

For most of the cardiac masses the treatment is excision. This serves the dual purpose of relieving symptoms and histological diagnosis. (35) Debulking of any mass should be as complete as possible. However, this is not possible in all cases and even when excision is thought to be complete, metastasis or recurrences have been reported.(1,2,8,12)

Adjunctive chemotherapy after surgery may be of benefit in tumors that are known to be sensitive or occur at multiple foci. (14, 25, 36) Radiotherapy also may be of help. (14, 36)

Heart transplantation has been successful for benign primary cardiac tumors. In the presence of a history of malignancy cardiac transplantation has been performed under two conditions. First, in patients with treated malignancies who have been disease free for some period of time. (37) Second, in patients with malignant primary heart neoplasms who do not have metastasis. (38) Currently 20 cases worldwide. (Rodríguez-Cruz, et al: Unpublished data) However, immunosuppressive therapy, necessary after the transplant, might promote the growth of micrometastasis already present at the time of surgery, or lead to the development of other malignancies, making heart transplantation a difficult therapeutic decision. (39-41)

Conclusion

In our opinion, judicious evaluation should be taken when evaluating and treating patients with heart tumors. Although it is really difficult for any group to get enough experience diagnosing and treating these patients due to the rarity of these neoplasms, it is important for every clinician to keep in mind the possibility of a cardiac tumor in the differential diagnosis of heart disease, especially in young patients. The diagnosis should be performed in a systematic way and aggressive and multidisciplinary treatment should be carried out in an attempt to improve survival.

Abstracto: *Tumores primarios del corazón son raros con una frecuencia de 0.0017% a 0.28%. Aquí reportamos un paciente masculino de 53 años con un sarcoma miofibroblástico primario del corazón que se presentó con una efusión hemorrágica en el pericardio. Se hace un repaso en la literatura y se presenta una breve discusión de la presentación clínica, diagnóstico y tratamiento de tumores cardíacos benignos y malignos.*

References

1. Lowry WB. McKee EE. Primary osteosarcoma of the heart. Cancer 1972; 30: 1068 73.
2. Yashar J, Witoszka M, Savage DD, et al. Primary osteogenic sarcoma of the heart. Ann Thorac Surg 1979; 28(6): 594-600.
3. Barnes AR, Beaver DC, Snell AM. Primary sarcoma of the heart: Report of a case with ECG and pathological studies. Am Heart J 1934; 9: 480.
4. Goldberg HP, Glenn F, Dotter CT, Steinberg I. Myxoma of the left atrium. Diagnosis made during life with operative and postmortem findings. Circulation 1952; 6: 762.
5. Crafoord CL, Case report. In: Lam CR, ed. Proceedings. International Symposium on Cardiovascular Surgery. Philadelphia, PA: WB Saunders Co. 1955: 202.
6. Reynen K. Frequency of primary tumors of the heart. Am J Cardiol 1996; 77: 107.
7. McAllister HA Jr. Tumours of the heart and pericardium. In: Silver MD, ed. Cardiovascular Pathology. 2nd ed. New York, NY: Churchill Livingstone Inc; 1991;2: 1297-1333.
8. Colucci WS, Schoen FJ, Braunwald E. Primary tumors of the heart. In: Braunwald E, ed. Heart Disease: A Textbook of Cardiovascular Medicine. 5th ed. Philadelphia, PA: WB Saunders Co; 1997; 42: 1464-1477.
9. Tillmanns H. Clinical aspects of cardiac tumors. Thorac Cardiovasc Surgn 1990; 38(SI); 152-56.
10. Lam KY, Dickens P, Chan ACL. Tumors of the heart. A 20 year experience with review of 12,485 consecutive autopsies. Arch Pathol Lab Med 1993; 117: 1027 31.
11. Tazelaar HD, Locke TJ, McGregor CGA. Pathology of surgically excised primary cardiac tumors. Mayo Clin Proc 1992; 67: 957-65.
12. Diflo T, Cantelmo NL, Haudenschild CC, Watkins MT. Atrial myxoma with remote metastasis: Case report and review ofthe literature. Surgery 1992; 111: 352-6.
13. Rettmar K, Stierle US, Sheikhzadeh A, Diederich KW. Primary angiosarcoma of the heart. Report of a case and review of the literature. Jpn Heart J 1993; 34: 667 83.
14. Loeffler H, Grille W. Classification of malignant

cardiac tumors with respect to oncological treatment. Thorac Cardiovasc Surgn 1990; 30 (Sl): 173-75.
15. Perroni D, Grecchi GL, La Ciura P, Landoni F. Right ventricular metastasis from choriocarcinoma: report of a rare case and review of the literature. Eur J Surg Oncol 1993; 19(4): 378-81.
16. Burke AP, Cowan D, Virmani R. Primary sarcomas of the heart. Cancer 1992; 69(2): 3,7-95.
17. Schrem SS, Colvin SB, Weinreb JC7 Glassman E, Kronzon I. Metastatic cardiac liposarcoma: Diagnosis by transesophageal echocardiography and magnetic resonance imaging. J Am Soc Echo 1990; 3: 149-53.
18. Mentzel T, Katenkamp D. [Myofibroblastic tumors. Brief review of clinical aspects, diagnosis and differential diagnosis]. (Abtr) Pathologe 1998; 19((3): 176-86.
19. Taccagni G, Rovere E, Masullo M, Christensen L, Eyden B. Myofibrosarcoma of the breast: review of the literature on myofibroblastic tumors and criteria for defining myofibroblastic differentiation. Am J Surg Pathol 1997; 21 (4): 489-96.
20. Mikuz G, Hofstadter F, Hausen A, Hager J. [The so-called cardiac myxoma. Histological, electronmicroscopical, immunofluorescence, and biochemical investigations in 3 cases]. Virchows Arch A Pathol Pathol Anat 1978; 380(3): 221-36.
21. Saha SP, Batchelder TL, Ira GH Jr. Resection of fibromyosarcoma pulmonary valve. Report of case. JFMA 1972; 59(4): 31-3.
22. Lestuzzi C, Nicolosi GL, Mimo R, Pavan D, Zanuttini D. Usefulness of transesophageal echocardiography in evaluation of paracardiac neoplastic masses. Am J Cardiol 1992; 70: 247-51.
23. Baumgartner R, Das S, Shea M, Le Mire M, Gross B. The role of echocardiography and CT in the diagnosis of cardiac tumors. International J Cardiac Imaging 1988, 3: 57-60.
24. Hausheer FH, Josephson RA, Grochow LB, et al. Intracardiac sarcoma diagnosed by left ventricular endomyocardial biopsy. Chest 1987; 92(1): 177-79.
25. Tracy DG, Zaloznik AJ. Primary cardiac angiosarcoma: A review and case report. Military Medicine 1991; 156(7): 372-74.
26. Aufiero TX, Pae WE Jr, Clemson BS, Pawlush DG, Davis D. Heart transplantation for tumor. Ann Thorac Surg 1993, 56: 1174-6.
27. Turner A, Batrick N. Primary cardiac sarcomas. A report of three cases and a review of the current literature. International J Cardiol 1993; 40: 115-9.
28. Shabetai R. Diseases of the pericardium. In: Schlant RC, Alexander RW eds. Hurst's. The Heart, Arteries and Veins. 8th ed. New York, NY: McGraw-Hill, Inc; 1997; 92: 1647-74.
29. Kaminer S, Truemper E. Hemopericardium and cardiac tamponade as presenting findings of anomalous left coronary artery syndrome complicated by transmural myocardial infarction. Pediatr Cardiol 1996; 17(30): 198-200.
30. Chou YH, Chen RL, Lin KH, Lin DT, Huang PH. Hemorrhagic pericardial effusion in beta-thalassemia major: report of a case. J Formos Med Assoc 191; 90(9): 867 70.
31. Tomkowski WZ, Szturmowicz M, Fijalkowska A, Burakowski J, Filipecki S. New approaches to management and treatment of malignant pericardial effusion. Support Care Cancer 1997; 5(1): 64-6.
32. Szturmowicz M, Tomkowski WZ, Fijalkowska A, Burakowski J, Filipecki S. The role of carcinoembriogenic antigen (CEA) and neuron-specific enolase (NSE) evaluation in pericardial fluid for the recognition of malignant pericarditis. Int J Biol Markers 1997; 12(3): 96- 101.
33. Davis S, Rambotti P, Grignani F. Intrapericardial tetracycline sclerosis in the treatment of malignant pericardial effusion: an analysis of thirty-three cases. J Clin Oncol 1984; 2(6): 631-6.
34. Tomkowski WZ, Filipecki S. Intrapericardial cisplatin for the management of patients with large malignant pericardial effusion in the course of the lung cancer. Lung Cancer 1997; 16(2-3): 215-22.
35. Takach TJ, Reul GJ, Ott DA, Cooley DA. Primary cardiac tumors in infants and children: intermediate and long-term operative report. Ann Thorac Surg 1996; 62(2): 559-64.
36. Nakamichi T, Fukuda T, Suzuki T, Kaneko T, Morikawa Y. Primary cardiac angiosarcoma: 53 months' survival after multidisciplinary therapy. Ann Thorac Surg 1997,63: 1160-1.
37. Armitage JM, Kormos RL, Griffith BP, Fricker FJ, Hardesty RL. Heart transplantation in patients with malignant disease. J Heart Transplant 1990; 9: 627-30.
38. Michler RE, Goldstein DJ. Treatment of cardiac tumors by orthotopic cardiac transplantation. Semin Oncol 1997; 24: 534-39.
39. Siebenmann R, Jenni R, Makek M, Oelz O, Turina M. Primary synovial sarcoma of the heart treated by heart transplantation. (letter) J Thorac Cardiovasc Surg 1990; 99(3): 567-8.
40. Crespo MG, Pulpón LA, Pradas G, et al. Heart transplantation for cardiac angiosarcoma: Should its indication be questioned? J Heart Lung Transplant 1993; 12: 527-30.
41. Couetil JP, McGoldrick JP, Wallwork J, English TAH. Malignant tumors after heart transplantation. J Heart Transplant 1990; 9: 622-6.

Reporte de Casos:

Brief Case Report
Metastatic Leiomyosarcoma of the Liver

Jorge W. Mayoral, M.D.

Abstract: *A case of metastatic leiomyosarcoma of the liver was presented. The clinical, radiological, pathologic and therapeutic aspects are mentioned.*

Case Report

This is a case of an 80 years old woman referred on December 3, 1990 by a primary physician because of anemia and positive stools for ocult blood. She had a barium enema which revealed diverticulosis of the colon. The anemia was not responsive to-parenteral iron therapy. No history of hematochezia or melena. No weakness or dizzy spells. No history of intake of non-steroidal intinflammatory agents. She had cholecystectomy 5 years earlier. On physical examination the only significant finding was a large mass, the size of a grapefruit in the pelvic area. It was hard, smooth and non-tender. Laboratory studies revealed: WBC: 7,100; RBC: 3.5: HGB: 7.6 gr.%; HCT: 26.7 vol.%; PL:count: 467.000. Upper endoscopy revealed a hiatal hernia. CT of the abdomen revealed a 24 x 16 x 9.7 cm. mass with central areas of necrosis and calcifications in the lower abdomen extending into the pelvis. A CT guided needle biopsy of the mass was reported as leiomyoma although sarcoma had to be considered. Abdominal operation revealed a tumor mass in the ileocecal area which was resected and a ileocolic anastomosis performed.

Final pathological report:

A- The specimen consists of a segment of small bowel, 40 cm in length and 3.5 cm in circunference- 16 cm from the margin of resection. There is an ovoid nodular mass attached to the serosa. The mucosa in this area is hyperemic. Upon sectioning the tumor it was light tan meaty and friable. Several enlarged lymph nodes were adjacent to the tumor mass. Dx. Malignant tumor.

The pathologic report was leiomyosarcoma, after several stain studies were done, with more than 10 mitosis per 10 HPF. She recovered from her operation but did not go for her follow up visits with the oncologist. In the interim she underwent panhysterectomy by her gynecologist for fibroma. In April 17, 1994 she was referred back from her gynecologist because of marked hepatomegaly and asthenia. The HGB was 12.5 gm% at that time. Needle liver biopsy of the liver revealed metastatic leiomyosarcoma. She received radiotherapy but succumbed few weeks later.

Discusion

Metastatic leiomyosarcoma of the liver is extremely rare although it has increased incidence in the patients with AIDS.(l) Leiomyosarcoma is said to be the commonest tumor arising from the Meckel's diverticulum.(l) It effects both sexes equally and has also been associated with Von Recklinghousen's disease, tuberous sclerosis and Peut-Jegher's polyps.(l) It accounts for approximately 20 % of small bowel malignacines in patient over age 20.(1) It is usually diagnosed late in the course of the disease when the primary lesion is diagnosed. The main symptoms are secondary to hemorrhage, intestinal obstruction or symptoms or signs secondary to the mass effect of the lesion in other organs. (1) The diagnosis can be suspected in the CT scan immages. (2) Metastatic lesions reveal a homogenous enhancement where as primary lesions reveal a heterogenous enhancement. Likewise there are two cytological patterns in the tumor: the spindle cell type and the epithelial type which may present some problems in the differential diagnosis with other tumors. The treatment of choice is surgical but when not feasible, chemoembolization is the second best alternative. (5) Chemotherapy is rather ineffective as well as radiotherapy. (4) Our patient presented with both, evidence of blood loss, and mass effect of the lesion. The CT scan although not definetly diagnostic was suggestive of leiomyosarcoma to the radiologist. The pathological specimen revealed a highly malignant lesion with more than 10 mitosis per 10 HP field.

Abstracto: *Un caso de leiomyosarcoma metastático al hígado fue presentado. Los aspectos clínicos, radiológicos, patológicos y terapéuticos fueron presentados.*

Bibliography

1. Preiser, Lantz P.C. Listron M.B., Davis M. Rilke F.O. Fenoglio, C.M.. Presien: Gastrointestinal Pathology, an Atlas and Text Ist. Ed. Raven Press 1989 547-551.
2. Soyer P: Blumke DA; Hruban RH; **Fishman EK** Hepatic leiomyosarcomas: CT features and pathologic correlation Eur J Radiol- Mar, 19(3) 177-82 1995.
3. Smith MB; Silverman JF; Reab SS; Toeli BD; Geisenger KR Fine-needle aspiration cytology of hepatic leiomyosarcoma Diagn. Cytopathol 1994 Dec; 11(4)321-7.
4. Soyer P; Blumeke DA: Riopel M; Hruban RH; Fishman EK Eur J Radiol 1955 Mar, 19(3) 177-82.
5. Mavligit GM: Zukwiski AA: Ellis LM: Chuang VP: Wallace S Gastrointestinal leiomyosarcoma metastatic to the liver. Durable tumor regresion by hepatic chemoembolization infusion with cisplatin and visblastine Cancer 1995 Apr 15; (8) 2083-8.

Aknowledgement:

I wont to thank Dr. Edgar C. Belmonte, pathologist for the interpretation of the slides.

Vol. 90 • 7-8-9-10-11-12 / 1998 • Pág. 135, 139

Reporte de Casos:

An Unusual presentation of Central Nervous System Lymphoma: A Case Report and Review of the Literature

*Edwin Rodríguez-Cruz, M.D.**
*Rosa M. Cintrón-Maldonado, M.D.***, Bernard A. Bercu, M.D., FACC****

Abstracto: *Linfoma primario del sistema nervioso central puede presentarse con una gran variedad de signos y síntomas. El caso de un hombre immunocompetente de 45 años de edad con linfoma primario del sistema nervioso central se reporta. Discusión del caso con énfasis en el diagnóstico diferencial de meningitis linfocítica, estrategias para el diagnóstico y fallas en el mismo se presentan.*

Case Presentation

The patient is a 45 year old white male, with previous history of hypertension, who presented to the Emergency Department with a 3 week history of headache, vascular in type, associated with numbness in the left side of his face. Neurologic examination was normal upon initial evaluation. Magnetic resonance imaging (MRI) of the head was normal except for the presence of a chronic inflammatory process involving the right mastoid sinus. The patient was discharged and referred to ENT for further evaluation and treatment of his mastoiditis. Two weeks later, he returned to the Emergency Department with acute onset of confusion, fever, nausea, vomiting, ataxia, headache and agitation. The physical examination on admission showed: HR= 90, regular; BP= 118/80 mmHg, without orthostasis; T= 101°F; RR= 25-30/ min. There was bilateral erythema of the tympanic membranes with fluid in the right middle ear. Neurological exam demonstrated slurred speech, left hemiparesis, left facial weakness, ptosis of the left eyelid and nystagmus on left lateral gaze. Plantar signs were extensor and clonus of both lower extremities was present. The lungs were clear. The remainder of the physical examination was within normal limits. Subsequently, he developed respiratory distress requiring intubation and admission to the Intensive Care Unit.

The patient only had mild peripheral leukocytosis. Laboratory investigations included a lumbar puncture, blood, sputum and urine cultures. (Table 1) Therapy was initiated empirically with ampicillin, ceftriaxone, dexamethasone and antimycobacterial medications. Other tests performed on the cerebrospinal fluid (CSF), as well as blood, serology and histology were non diagnostic. MRI of the brain showed mild diffuse meningeal enhancement and the suggestion of a small communication from the right mastoid sinus and the epidural space near the sigmoid sinus. A high resolution computed tomographic (CT) scan of the brain supported this finding. The patient then underwent right mastoidectomy and bilateral myringotomy with pneumatic tube placement. No macroscopic communication was found during surgery. He showed improvement in mentation and some improvement in his neurological deficits and was discharged 2 weeks after admission. His medications on discharge included: amoxicillin/clavulanate, pyrazinamide, ethambutol, isoniazid, rifampin, prednisone, niacin and multivitamins.

On a follow up visit, 3 weeks later, he presented transient loss of temperature discrimination on the right side of his body and dizziness. His dysphagia had improved but his appetite was poor. His physical examination revealed orthostatic changes in blood

Corresponding author:
**Fellow Cardiology, Children's Hospital of Michigan Wayne State University - Detroit, Michigan*
Secondary authors:
***Dept. of Combined Internal Medicine and Pediatrics Saint Joseph Mercy Oakland - Pontiac, Michigan*
****Clinical Associate Professor of Medicine Wayne State University School of Medicine Director, Dept. of Combined Internal Medicine & Pediatrics Saint Joseph Mercy Oakland - Pontiac, Michigan*

Originating Institution: Department of Combined Internal Medicine and Pediatrics Saint Joseph Mercy-Oakland Pontiac, Michigan
Address for reprints: Edwin Rodríguez-Cruz, M.D. Work: Division of Cardiology Children's Hospital of Michigan 3901 Beaubien Blvd. Detroit, Michigan 48201-2196
Tel: (313) 745-5484 (secretary) Beeper: (313) 745-5111 #7917 Fax: (313) 993-0894 E-Mail: ERODRI@pol.net

pressure and pulse and weight loss, but no evidence of dehydration. A cortisol level to rule out adrenal insufficiency was normal. A repeat lumbar puncture was performed. (Table I) All previous laboratory studies were repeated, in addition to ANA, Rheumatoid Factor and oligoclonal bands that were non diagnostic. High resolution. CT scan of the brain was performed the following day and revealed hydrocephalus and a left cerebellar lesion interpreted as compatible with an abscess or tuberculoma adjacent to the fourth ventricle. The patient was re-admitted to the hospital and became obtunded the next day. Treatment with intravenous dexamethasone, ceftriaxone, and metronidazole plus the anti-tuberculous medications was continued. A ventriculostomy catheter was inserted into the right lateral ventricle and a biopsy of the dura was obtained that showed normal tissue. Repeated CSF studies and cytology were non-diagnostic again. One week later, a follow up CT scan demonstrated a new lesion in the left temporal lobe. A CT scan guided needle biopsy of the temporal lobe lesion was obtained and a pathological diagnosis with immunoperoxidase stains revealed a large B cell type malignant lymphoma. Repeated cytology of the CSF at this time confirmed malignant cells consistent with central nervous system lymphoma (CNS-L).

Table 1.
Laboratory evaluation of the patient

Cerebrospinal Fluid	First Lumbar Puncture*	Second Lumbar Puncture+
WBC cells/mm3	161	298
Lymphocytes %	96	97
Monocytes %	4	3
Neutrophils %	0	0
Proteins mg/dl	675	748
Glucose mg/dl	20	22
Gram Stain	no organisms	no organisms
Latex Agglutination	negative	negative
India Ink	negative	negative
Cytology	negative	negative

*, + Other cultures or tests performed which were negative or non-diagnostic: Polymerase Chain Reaction for tuberculosis and Herpes, Lymphocytic Choriomeningeal Virus, Sporothrix, Cryptococcus, Coccidioides, Q fever, fungal and other viruses. Serum complement, VDRL and Lyme's serology. HIV, Angiotensin Converting Enzyme Level and Immunoglobulins levels.

Key
* at initial presentation
+ 3 weeks later

Chemotherapy and radiotherapy was instituted, however, the patient died 6 months after the onset of symptoms. In post-mortem examination a total of 5 cerebral lesions were identified, 3 not previously noted on MRI or CT scan.

Discussion

Lymphocytic meningitis and lymphoma

Bacterias, fungi, viruses and parasites should be considered in the differential diagnosis of lymphocytic meningitis as well as sarcoidosis, demyelinating diseases, rheumatologic diseases, and neoplasms, including lymphoma. (Table 2)

Table 2.
Common Etiologies and Differential Diagnosis of Lymphocytic Meningitis

Bacterial	Mycobacterium, Treponema, Leptospira, Actinomyces, Arachnia, Borrelia, Brucella
Fungi	Cryptococcus, Candida, Coccidioides, Histoplasma, Blastomyces, Sporothrix, Cladosporium
Viral	Lymphocytic Choriomeningeal virus, HTLV-III, Echovirus, Herpes
Parasites	Toxoplasma, Cysticercosis
Non infectious	Noeplasm, Sarcoidosis, Multiple Sclerosis, Granulomatous arteritis, Rheumatologic Diseases with neurological involvement
CSF Low Glucose	mycobacterial, syphilis, Cryptococcus, leukemia, metastatic carcinoma, sarcoidosis, lymphoma
CSF High Protein	bacterial meningitis, bloody tap, cord tumors, brain tumors polyneuritis

KEY
CSF- cerebrospinal fluid
HTLV- Human T lymphocyte Virus

Lymphomas are a group of neoplasms of the reticuloendothelial and lymphatic systems. Literature indicates a male to female ratio from 1.5:1 to 2.5:1. (1, 2) The clinical presentation depends upon the site of the primary tumor. The most common locations are lymph nodes, breasts, thorax and abdomen. Less common places of involvement include the central nervous system (CNS), intraocular (3), heart (4), stomach (5), prostate (6), endobronchial (7), uterus (8), and lacrimal ducts (9). The major classifications are Hodgkin's and Non-Hodgkin's lymphomas; other less common types include Burkitt's lymphoma (10), and mycosis fungoides (11). All have been reported in the CNS.

The first description of a CNS-L was reported by Bailey in 1929. (12) In the mid 1980's, Spaun, et al. (1)

QIPRO MIRANDO EL NUEVO

Durante 25 años, y bajo la encomienda otorgada por el Gobierno Federal (HCFA)*, QIPRO ha estado sirviendo a la sociedad puertorriqueña protegiendo y promoviendo la Calidad de los Servicios de Salud que reciben los Beneficiarios de Medicare. A través de sus proyectos para mejorar la calidad y en colaboración con la comunidad médica y hospitalaria, se han logrado avances favorables.

Los siguientes son algunos proyectos que fueron llevados a cabo con EXITO con la colaboración de varias instituciones hospitalarias y sus respectivas facultades médicas; un modelo único de lo que se puede lograr coordinando esfuerzos.

UNSTABLE ANGINA MANAGEMENT

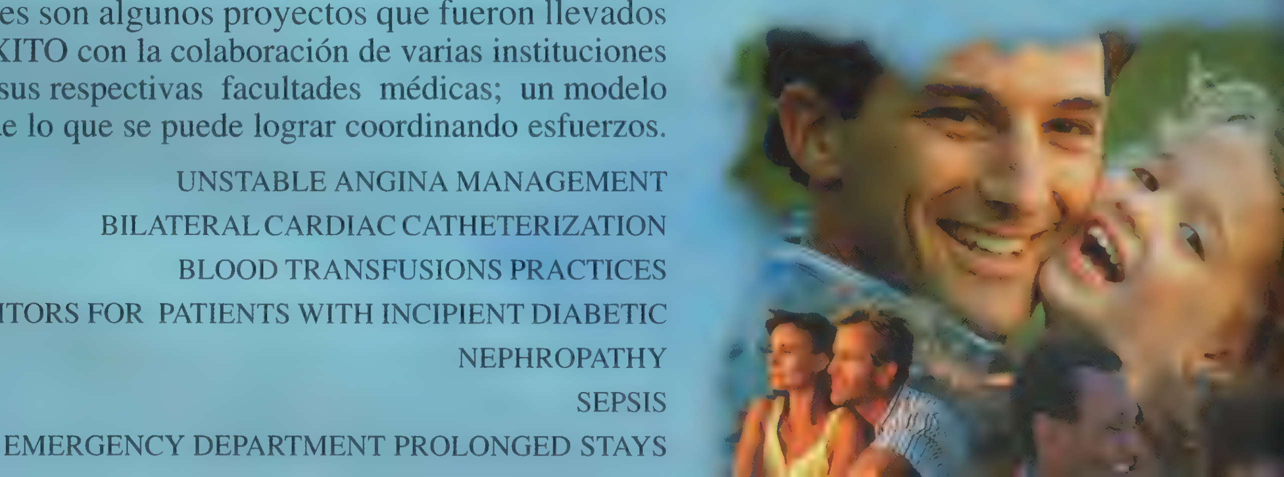
BILATERAL CARDIAC CATHETERIZATION

BLOOD TRANSFUSIONS PRACTICES

USE OF ACE INHIBITORS FOR PATIENTS WITH INCIPIENT DIABETIC NEPHROPATHY

SEPSIS

EMERGENCY DEPARTMENT PROLONGED STAYS





Debido a la alta incidencia de ciertas enfermedades en los beneficiarios, HCFA ha decidido continuar el estudio de los procesos de cuidado de éstas con el propósito de seguir mejorando los mismos a medida que las ciencias clínicas van ofreciendo nuevos enfoques.

Areas de estudio de PROYECTOS para los años 2000 - 2003

Proyectos a nivel nacional

Acute Myocardial Infarction
Heart Failure
Pneumonia
Stroke / Transit Ischemic Attack / Atrial Fibrilation
Diabetes
Breast Cancer
Otros Proyectos a nivel local

Q PRO

*(Health Care Financing Administration)

found the incidence of primary malignant CNS-L to be 1.83 per million per year; comprising from 0.85% to 2.3% of all primary tumors of the CNS. This incidence has risen in the immunocompromised population as well as in the general population in the last 20 years. (13- 15) It may occur at any age, with a higher incidence during the 5th to 7th decade of life. (16, 17) The majority of CNS-L are B-cell type with aggressive histologic changes.(18, 19) The median survival is less than 2 years with conventional therapy.(19)

Clinical presentation

Due to the diffuse and multifocal infiltrative nature of the lesion the clinical presentation of primary CNS-L is highly variable. (17) Various authors report the frontal and temporal lobes, cerebellum, basal ganglia, brain stem and corpus callosum as predilected sites for CNS-L. (1, 20, 21) In our patient the five lesions found on post mortem examination involved the left frontal lobe (2 lesions), left temporal lobe (1 lesion), and left cerebellum (2 lesions). Three of the lesions were not seen on prior CT or MRI scans of the brain.

The signs and symptoms of CNS-L are multiple and non specific from the onset of disease. Central symptoms are: speech problems, headache, weakness, vomiting, amnesia, somnolence and convulsions. (15, 18) Signs may include: papilledema and altered state of consciousness among others. (15, 22) In our case, the early finding of bilateral mastoiditis, fever, peripheral leukocytosis, CSF Iymphocytosis, low CSF glucose with high CSF protein suggested an infectious etiology. Subsequent clinical improvement with antibiotic and antimycobacterial treatment was consistent with this diagnosis. Also, the new onset of orthostatic blood pressure changes suggested adrenal insufficiency, complication described with histoplasmosis and with systemic and CNS tuberculosis, nevertheless adrenal insufficiency was ruled out. (23-26) However, after 3 weeks of therapy, improvement was minimal and further evaluation was undertaken. With the discovery of a left cerebellar lesion the possibility of an abscess or tuberculoma was raised, and treatment with intravenous steroids, antibiotics and antimycobacterial medications was pursued. (27) A repeat CT scan of the brain, 1 week later, demonstrated a new left temporal lobe lesion. The possibility of a CNS-L was considered and a biopsy obtained, confirming the diagnosis.

Retrospectively, Pel-Epstein fever (28) could have explained the patient's pyrexia; the orthostasis was probably an autonomic effect due to the invasion of the neoplasm, but this is speculative. The lymphocytic meningitis is not an uncommon presentation for CNS-L. The neurological deficits at presentation are several and well discussed in the literature. However, in the literature reviewed by us no report was found that described the loss of temperature discrimination or hypotension as a presentation or complication of CNS-L.

Diagnosis and treatment

Many of the techniques used to establish the diagnosis of CNS-L are not specific. Extensive radiological investigation has been used including MRI with and without gadolinium (29), CT scan, 1 8F-fluoro-2-deoxyglucose- positron emission tomography (FDG-PET) (30), and 201 TI single-photon emission computed tomography (SPECT) (31). Most of these investigations are helpful only in demonstrating a mass lesion, although some of them try to characterize the lesions metabolically. In our case though, serial high resolution CT scan and MRI failed to show 3 of the lesions, all of them measuring 0.5 mm or more.

Cytology of CSF has a low yield. (32) PCR examination of the CSF have been used to compliment conventional cytology in the diagnosis. (33) The use of immunohistochemistry, cytogenetics, ultrastructural analysis, molecular biology studies, and frozen biopsy samples provide further aid in arriving at the diagnosis. (32, 34-36) While biopsy of the lesion is the ultimate diagnostic tool, still some cases are only discovered at autopsy despite extensive evaluations. (37)

The treatment of lymphoma includes surgical resection, radiation, intrathecal and systemic chemotherapy. Surgery by itself does not affect outcome. (17, 19) The combination of chemotherapy and radiotherapy carry a high toxicity, especially if used repeatedly. (38) However, with new modalities of radiotherapy improvement in outcome may occur. (16, 39) Steroids have shown to be useful. Alone they could produce clinical and radiological remission. (40) On the other hand response could be transient. (32) Retrospectively, we think that the use of dexamethasone and prednisone was the reason for the initial improvement in our patient's condition. Although spontaneous regression and recurrence of CNS-L have been reported. (41)

Conclusion

The presentation and progress of this case reaffirm the importance of persistence in the evaluation and follow up of a patient with lymphocytic meningitis when only partial improvement is obtained. The suspicion for malignancy should increase in such a case. CSF histochemical evaluation appears to be of utmost importance and finally biopsy must be a consideration.

References

1. Spaun E, Midholm S, Tinggasrd-Pedersen N, Ringsted J. Primary malignant lymphoma of the central nervous system. Surg Neurol 1985; 24: 646-650.

2. Cool CD, Bitter MA. The malignant lymphomas of Kenya: morphology, immunophenotype, and frequency of Epstein-Barr virus in 73 cases. Hum Pathol 1997; 28(9): 1026-33.

3. Brown SM, Jampol LM, Cantrill HL. Intraocular lymphoma presenting as retinal vasculitis. Survey of Ophthalmology 1994 Sept-Oct; 39(2): 133-140.

4. Yuh DD, Kubo SH, Francis GS, et al. Primary lymphoma treated with orthotopic heart transplantation: a case report. J Heart Lung Transplant 1994; 13: 538-42.

5. Stephen MR, Farquharson MA, Sharp RA, Jackson R. Sequential malt lymphomas of the stomach, small intestine, and gall bladder. J Clin Pathol 1998, 51(1): 77-9.

6. Leung TW, Tung SY, Sze WK, Tsui WC, Wong MK, O SK. Primary non-Hodgkin's lymphoma of the prostate. Clin Oncol (R Coll Radiol) 1997; 9(4): 264-6.

7. Reina Zoilo JJ, Ruiz Borrego M, Valenzuela Claros JC, et al. Primary endobronchial non Hodgkin's lymphoma: description of a case and review of the literature. An Med Interna 1998; 15(2): 97-9.

8. Kaito K, Otsubo H, Sekita T, et al. Primary non-Hodgkin's lymphoma of the uterine cervix complicated by acute renal failure due to ureter obstruction. (Abstr) Rinsho Ketsueki 1998; 39(6): 463-5.

9. Nakamura K, Uehara S, Omagari J, et al. Primary non-Hodgkin's lymphoma of the lacrimal sac: a case report and review of the literature. Cancer 1997; 80(11): 2151 -5.

10. OstronoffM, Soussain C, Zambon E, et al. Burkitt's lymphoma in adults: a retrospective study of 46 cases. (Abstr) Nouv Rev Fr Hematol 1992; 34(5): 389-397.

11. Filipe PL, Coutinho VS, Canhao P, et al. Mycosis fungoides with early central nervous system involvement. Acta-Dermato-Venerologica 1994 Jan, 74(1): 63-64.

12. Bailey P. Intracranial sarcomatous tumours of leptomeningeal origin. Arch Surg 1929; 18: 1359-1402.

13. Deangelis LM. Current management of primary central nervous system lymphoma. Oncology 1995; 9(1): 63-71.

14. Eby NL, Grufferman S, Flanelly CM, et al. Increasing incidence of primary brain lymphoma in the US. Cancer 1988; 62: 2461-2465.

15. Pittman KB, Olweny CLM, North JB, Blumbergs PC. Primary central nervous system lymphoma. A case report and review of the literature. Oncology 1991 ;48: 184- 187.

16. Sheik B, Siquiera E. Primary lymphoma of the central nervous system. Br J Neurosurg 1994; 8(4): 427-432.

17. Sharma S, De S, Fernandes P, et al. Primary lymphoma of the brain- a report of 5 cases and review ofthe literature. Indian J Cancer 1991; 75(28): 75-80.

18. Grove A, Vyberg M. Primary leptomeningeal T-cell lymphoma: a case and a review of primary T-cell lymphoma of the central nervous system. Clin Neuropath 1993; 1(12):7-12.

19. O'Neill BP, Illig JJ. Primary central nervous system lymphoma. Mayo Clin Proc 1989; 64(8): 1005-1020.

20. Jellinger K, Radaskiewicz TH, Slowik F. Primary malignant lymphomas of the central nervous system in man. Acta Neuropath (Berlin) 1975; Suppl. VI: 95-102.

21. Spillane JA, Kendall BE, Moseley IF. Cerebral lymphoma: clinical radiological correlation. J Neurol Neurosurg Psychiatry 1982; 45(3): 199-208.

22. Mackenzie RA, Braye SG. Primary lymphoma of the central nervous system: a case report. Clin Exp Neurol 1979; 16: 139- 148.

23. Matah SC, Kesharwani GL, Srivastava GN, Singh SK, Agrawal JK. Adrenocortical insufficiency in smear positive pulmonary tuberculosis. Indian J Chest Dis Allied Sci 1992 Ju1; 34(3): 133-136.

24. Davenport J, Kellerman C, Reiss D, Harrison L. Addison's disease. Am Fam Phys 1991 Apr; 43(4): 1338-1342.

25. Hull PR. Systemic histoplasmosis with oesophageal obstruction due to Histoplasma granulomas. Successful treatment with rifampicin and amphotericin B. S Afr Med J 1979 Apr 14; 55(16): 639-640.

26. Morgan HE, Austin JH, Follet DA. Bilateral adrenal enlargement in Addison's disease caused by tuberculosis. Nephrotomographic demonstration. Radiol 1975 May; 115(2): 357-358.

27. Hejazi N, Hassler W. Multiple intracranial tuberculomas with atypical response to tuberculostatic chemotherapy: literature review and a case report. Acta Neurochir (Wien)1997; 139(3): 194-202.

28. Scanlon GT, Castellino RA, Rudders R. Lymphographic demonstration of cyclic changes in lymph nodes size during Pel-Epstein fever. Cancer 1975, 36(6): 2026-8.

29. Gupta RK, Gupta S, Mittal P, et al. Unusual enhancement on gadolinium-enhanced MRI in a case of primary cerebral lymphoma. Neuroradiology i993, 35(6): 454-456.

30. Hoffman JM, Waskin HA, Schifter T, et al. FDG-PET in differentiating Iymphoma from non malignant central nervous system lesions in patients with AIDS. J Nuclear Med 1993; 34(40): 567-575.

31. O'Malley JP, Ziessman HA, Kumar PN, et al. Diagnosis of intracranial Iymphoma in patients with AIDS: value of 201 Tl single-photon emission computed tomography. AJR Am J Roentgenol 1994 Aug; 163(2): 417-421.

32. Neuwelt EA, Fraenkel EP, Gumerlock MK, Braiziel R, Dana B, Hill SA. Developments in the diagnosis and treatment of primary CNS Iymphoma. Cancer 1986, 58: 1609- 1620.

33. Rhodes CH, Glantz MJ, Glantz L, et al. A comparison of polymerase chain reaction examination of cerebrospinal fluid and conventional cytology in the diagnosis of lymphomatous meningitis. Cancer 1996; 77(3): 543-548.

34. Collin KA, Davis GJ. Angiotropic large cell lymphoma. South Med J 1995 Feb; 88(2): 235

35. Lachance DH, O'Neill BP, Mac Donald DR, et al. Primary leptomeningeal Iymphoma: report of 9 cases, diagnosis with immunocytochemical analysis, and review of the literature. Neurology 1991; 41(1): 95-100.

36. Miller DC, Najjar S, Budzilovich GN. Neuropathology of AIDS in surgical biopsy specimens. Neurosurg Clin N Am 1994; 5(1): 57-70.

37. Taratuto AL, Sevlever G, Piccardo P. Clues and pitfalls in stereotactic biopsy of the central nervous system. Arch Pathol & Lab Med 1991 Jun; 115(6): 596-602.

38. Waterson J, Toogood 1, Nieder M, et al. Excessive spinal cord toxicity from intensive central nervous system-directed therapies. Cancer 1994 Dec 1, 74 (11): 3034-3041.

39. Tait DM. Pediatric radiotherapy. Curr Opin Peds 1993 Feb; 5(1): 117-123.

40. Vakili ST, Muller J, Shidnia H, Campbell RL. Primary lymphoma of the central nervous system: a clinicopathological analysis of 26 cases. J Surg Oncol 1986; 33(2): 95-102.

41. Heinzlef O, Poisson M, Delattre JY. Spontaneous regression of primary cerebral lymphoma. (Abstr) Rev Neurol (Paris) 1996; 152(2): 135-138.

Vol. 90 • 7-8-9-10-11-12 / 1998 • Pág. 140, 143

Artículos de Repaso:

Hereditary Colorectal Carcinoma Syndromes and Their Implications for Colorectal Carcinoma in Puerto Rico

Rafael A. Mosquera, M.D. and Henry T. Lynch, M.D.***

Abstract: *During the last 41 years cancer of the colon in Puerto Rico has markedly increased as reported by the Puerto Rico Cancer Registry. The etiology of this increase remains elusive, but possibilities include an increase in reporting new cases, dietary modifications, exposure to carcinogens, as well as an hereditary predisposition. The importance of Hereditary Nonpolyposis Colorectal Cancer (HNPCC) in Puerto Rico, its molecular genetics, diagnostic criteria, and management will be discussed.*

Introduction:

Since 1950, the incidence of colorectal carcinoma (CRC) in Puerto Rico has increased in males from 5.4 to 28.2 and in females from 6.4 to 24.7 (crude and age adjusted with 1970 Puerto Rico, Census Population)(1). This is a 5 fold increase in males and almost a 4 fold increase in females for a period of 21 years. CRC is the second most common cancer in Puerto Rico for males and the third for females . From the 2,548 male cancer deaths in 1991, 7% were from cancer of the colon, and from 1724 cancer deaths in women, 8% were from cancer of the colon (1). Cancer of the gastrointestinal tract was the third leading cause of death by cancer in male and females in Puerto Rico. The number of crude rates for this cancer are consistently increasing both for males and females.

CRC is the fourth most frequent malignancy worldwide (after cancer of the lung, stomach, and breast in 1985), with an estimated 678,000 cases occurring that year. Its mortality that year was 394,000, making it the third leading cause of cancer mortality in the world (2,3).

In the USA, it is projected that CRC will account for approximately 131,600 new cases and 56,500 deaths in 1998(4), ranking as the second leading cause of cancer mortality among men and women combined. In 1990, large bowel malignancies in that country accounted for 758,000 years of life lost prematurely (2).

For the year 2000, we expect approximately 1103 new cases of colorectal carcinoma in Puerto Rico of which 66 (6%) will have been preventable do to early detection through knowledge of its hereditary nature.

Discussion:

As described previously, colon cancer incidence has been progressively increasing since 1950 in Puerto Rico, as well as in the rest of the world. Many factors have been implicated in this increase. These findings have been possible since in Puerto Rico by law all cases of cancer have to be reported to the Puerto Rico Cancer Registry. Changes in the diet and hereditary component may be contributory factors to CRC's increased incidence.

1. *Increased in reporting of new cases:*

Since the development of the registry the cases of colorectal carcinoma being reported has been slowly increasing, do to better efficiency in communications as well as better techniques to obtain, store and analyze the data.

2. *Dietary factors:*

During approximately 40,000 generations (millions of years) the human diet was based on food obtained mainly from vegetables (5).

Food came from the roots and fruits, which contained a large quantity of phytocomponents which provided protection for cardiovascular diseases and cancer. For generations the organism adapted genetically to this type of diet.

In approximately 200 years (8 generations), with the development of the industrial revolution, the diet began to change. Rich fiber food was processed and the quantity of fiber in it decreased markedly. The quantity of fat in food increased, as well as the total energy; meat was transformed in a symbol of opulence in our society.

**Gastroenterologist, Director of the Hereditary Nonpolyposis Colorectal Carcinoma Registry at Ryder Memorial Hospital, Humacao, Puerto Rico*
***Oncologist. Professor and Chairman, and Professor of Medicine at Creighton University. Director of the Department of Preventive Medicine and Public Health and of the Hereditary Cancer Institute at Creighton University in Omaha, Nebraska.*

This change in human's diet, from one based on vegetables to one with an increased in animal products (characterized by high fat and low fiber content), was accompanied by a marked change in the types of diseases. Cancer, diabetes mellitus, cholelithiasis, varices, obesity and cardiovascular diseases begin to predominate. It has been shown in experimental animals, that a low fiber diet causes an increased in colon cancer. Observations in human populations from developed countries also show an increase in colon cancer incidence due to low fiber, high animal fat diet (6).

Since 1950 the population of Puerto Rico has developed a change in its dietary components changing from a high fiber and relatively low fat diet to a low fiber and high fat diet. We speculate that this dietary change might be one of the factors in the dramatic increase of CRC in Puerto Rico.

3. Hereditary component:

Primary genetic factors were first observed by Warthin in 1913 when he described the "Family G"(7). Family members were found to have hereditary colorectal, stomach, and endometrial carcinomas. All his original records were given to Lynch and Krush and used to update "Family G" (8). In 1966, Lynch described the aggregation of CRC and stomach and endometrial tumors as etiologic in at least 5 -10% of patients with colon cancer (9). Burt (10) has described familial clustering of CRC, and he estimates that about 6% of CRC cases may manifest HNPCC.

HNPCC variants have been designated as Lynch syndromes I and II. Lynch syndrome I (site specific) is characterized by CRC at young age (mean age 44 y/o), predominance of proximal colon cancers (70% proximal to the splenic flexure) increased frequency of synchronous and metachronus CRC's (30% metachronous CRC within 10 years following less than subtotal colectomy for initial CRC) and an autosomal dominant mode of inheritance. Lynch syndrome II has all of the aforementioned features but also includes an increased frequency of extracolonic cancers particularly of the endometrium, followed by adenocarcinoma of the ovary, and transitional cell carcinoma of the ureter and renal (11 - 14).

The etiology of HNPCC results from germ-line mutations of genes involved in DNA nucleotide mismatch repair, including *hMSH2, hMLH1* (15), *hPMS2* and *hMSH6* (16). The most common is hMSH2 seen in 50% of patients with HNPCC.

Criteria for HNPCC were established by the International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer (17) and are known

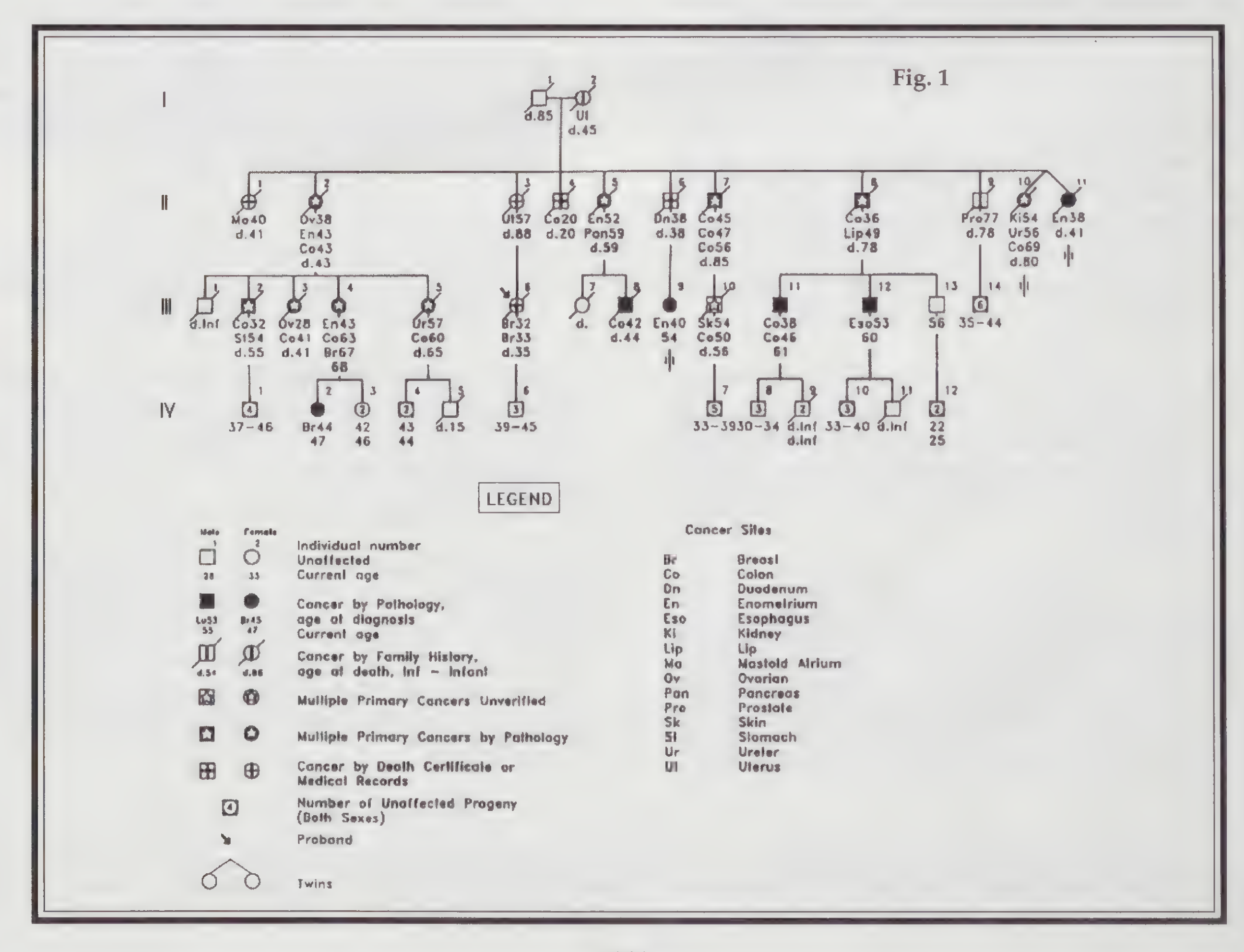


Fig. 1

as the "Amsterdam Criteria". They are as follows: 1.) three or more relatives with histologically verified CRC, one of whom is a first-degree relative of the other two; 2.) CRC involving at least two generations; and 3.) one or more CRC cases diagnosed before age 50 (Figure 1 and 2)

It has been shown in HNPCC families that an adenoma is usually the precursor lesion for CRC (11,18,19). Therefore, the recommendations are that subjects at 50% risk have a surveillance colonoscopy initiated at age 25. Colonoscopy should be repeated at 2-year intervals through age 35 and then every 1 to 2 years (10,11).

When a patient is known to be the carrier of an HNPCC germ-line mutation, we recommend annual colonoscopy. As shown by Jarvinen (20) and more recently, by Vansen et.al. (21) , colonic screening significantly decreases the incidence of CRC by as much as 62% in healthy individuals from families with HNPCC. Also lesions are identified at earlier stage (Dukes A or B). Its recommended that once CRC is identified subtotal colectomy should be performed because of the risk of multiple CRC (10).

As previously mentioned, patients with the Lynch syndrome II variant need to be closely observed for the development of extracolonic malignancies. Its recommended that annual endometrial vacuum curettage be initiated at age 30.

In both variants, education and genetic counseling should be initiated at the teen years (10,11). Women who have CRC, particularly if early onset and if they harbor an HNPCC mutation, should be told of the option for prophylactic total abdominal hysterectomy and bilateral salpingo-oophorectomy once their families have been completed (10,11).

Conclusions:

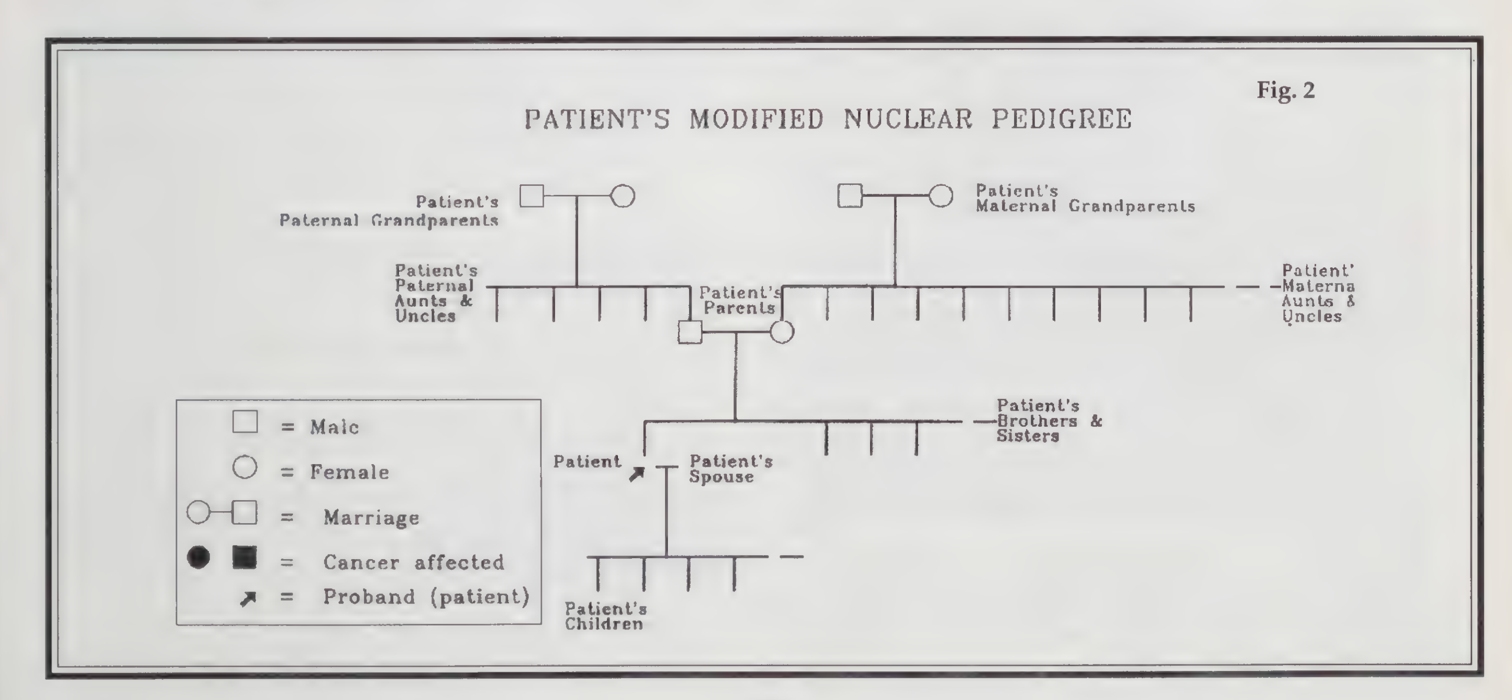
The incidence of CRC in Puerto Rico, as well as in developed countries, has been progressively increasing over the last 21 years. This can be secondary to better information gathering or reporting or to hereditary factors, but mainly to the low fiber, high fat intake in our society.

The European Community, through its Europe Against Cancer program, has developed guidelines on dietary prevention of CRC. In Britain the National Advisory Committee on Nutritional Education, and in the USA the Department of Agriculture have developed the food guide pyramid to orient the population toward "Eating Right". All have recommended, in their diet guidelines, eat lean, eat coarse (or unrefined), eat in moderation, cut down on salt and sugar and reduce alcohol intake.

Puerto Rico should reevaluate its main dietary components, specially at younger ages, to include a higher intake of fiber and lower in fats, as to prevent the development of cardiovascular diseases, diabetes, obesity and CRC.

In spite of advances in treatment, only 50% of persons newly diagnosed with CRC will be alive in 5 years . Even successful treatment of large bowel cancer incurs substantial economic and psychologic cost (4,6).

Aggressive screening of CRC and preventive dietary orientation have the potential to ameliorate CRC's morbidity and mortality.



The hereditary component of CRC should be evaluated by doing pedigrees of those families with CRC at young ages (Figure 1) including metachronous CRC, multiple primary cancers, and patients with multiple relatives with CRC and/or HNPCC's extra-colonic cancers (Figure 2). Once high-risk patients are identified, screening techniques can be applied and hopefully lead to the detection of the malignant lesions at earlier stages (22) or even prevent them by prophylactic surgeries, improving the survival of this usually young patients.

For this purpose an HNPCC Registry has been developed at Ryder Memorial Hospital in Humacao. Our mission is to identify families with HNPCC by physician or self referral. Pedigrees will be constructed that will identify HNPCC (or other hereditary cancer syndromes) so that patients at increased risk might benefit from genetic counseling and DNA testing, as well as highly targeted surveillance and management strategies. For more information about the Registry and for referral of patients contact the following Internet Address: **http://netdial.caribe.net/~mosquera/.**

Abstracto: *En los ultimos 41 años la incidencia de cancer de colon en Puerto Rico a aumentado drasticamente, segun reportado en el Registro de Cancer de Puerto Rico. Entre las posibles causas de este aumento, tenemos un aumento en el reporte de los casos a el registro, modificaciones en la dieta, exposicion a carcinogenos y finalmente la predisposicion genetica. La importancia del sindrome de cancer de colon hereditario no asociado a poliposis en Puerto Rico, su genetica molecular, los criterios diagnosticos y su manejo son discutidos ampliamente.*

Bibliography:

1. Departamento de Salud de Puerto Rico. "Cancer in Puerto Rico 1991" Published by The Central Cancer registry of Puerto Rico Nov. 1993 3-26; 41-154
2. Miller, B. A., Ries, L., Hmkey,B. et. al. (1993) Cancer Statistics Review: 1973-1990, National Cancer Institute, NIH publication no. 93-2789
3. Whale, S. J., Parkin, S. and Masayer (1990) Patterns of Cancer Incidence in five continents. Lyon International Agency for Research on Cancer.
4. Landis, S. Murray, T. Bolden, S. and P. Wingo (1998) Cancer statistics, 1998 CA: A Cancer Journal for Clinicians 48; 6 - 29.
5. Alabaster, O. Tang, Z. and Shivapurkar, N. (1996) Dietary fiber and the chemopreventive modulation of colon carcinogenesis. Mutation Research 350 (1) 185 - 197
6. Schatzkin, A. (1997) Dietary Prevention of Colorectal Cancer. From Prevention and early Detection of Colorectal Cancer. edited by Young, G, Rozan, P. and B. Levin
7. Warthin A.S. (1913) Heredity with reference to carcinoma. Arch. Intern. Med. 12;546-555
8. Lynch, H. and Krush, A. J. (1971) Cancer family "G" revisited: 1985 - 1970 Cancer, 27: 1505 - 1511.
9. Lynch, H., Shaw, M., Magnuson, C. et. al. (1966) Hereditary factors in two large midwestern kindreds. Arch. Inter. Med.117: 206-212
10. Burt,R. and G.Petersen (1997) Familial Colorectal Cancer: Diagnosis and Managment. From Prevention and Early Detection of Colorectal Cancer. edited by Young, G. ,Rozan,P. and B. Levin.
11. Lynch, H., Smyrk, T., Cavaliery, J. and J. Lynch (1994) Identification of an HNPCC Family. Ame. Journ. Gastroenterology vol. 89: 4 : 605-609.
12. Lynch, H. and Lynch, J., (1995) Lynch Syndromes I and II. In: Cohen, A. Winawer, S., Friedman, M. et. al. Cancer of the Colon, Rectum and Anus. McGraw - Hill 61-82.
13. Lynch, H. Ens, J., Lynch, J. et al. (1988) Tumor Variation in three extended Lynch Syndrome II kindreds. Am. J. Gastroenterology; 83: 741-747.
14. Lynch, H., Shuelke, G., Kimberling, W. et.al. (1985) Hereditary nonpoliposis colorectal cancer (Lynch I and II). I Clinical description resource. II Biomarker studies. Cancer 56(4); 934-938; 939-951.
15. Fishel, R. Lescoe, M. Rao, M. et. al. (1993) The human gene homolog MSH2 and its association with hereditary nonpolyposis colon cancer. Cell 75; 1027 - 1038.
16. Miyaki, M, Konishi, M, Tanaka, K. et. al. (1997) Germline mutation of MSH6 as the cause of hereditary nonpolyposis colorectal cancer. Nat.Genet. 17:271-272.
17. Vasen, H., Meclin, J. , Meera, K. and H. Lynch (1991) The International Collaborative on Hereditary Non Polyposis Colorectal Cancer. Diss. Colon Rectum; 34: 424 - 425.
18. Lanspa, S. Lynch,H. Smyrk, T. et.al. (1990) Colorectal adenomas in the Lynch syndromes. Results of a colonoscopy screening program. Gastroenterology 98; 1117 - 1122.
19. Lanspa, S., Jenkins, J. and P. Watson (1993) Adenoma follow up in at risk Lynch syndrome family members. Anticancer Res. 13; 5C: 1793 - 1794.
20. Jarvinen, H., Mecklin, J. and P. Sistonen (1995) Screening Reduces Colorectal cancer rates in families with Hereditary Nonpolyposis Colorectal Cancer. Gastroenterology 108; 1405 - 1411.
21. Vansen, H. Van Ballegooijen, M., Buskens, E. et.al. (1998) A cost effectivness analysis of colorectal screening of hereditary nonpolyposis colorectal carcinoma gene carriers. Cancer 82: 1632-1637.
22. Parkin, D. , Pisani, P. and P. Ferlay (1993) Estimates worldwide incidence of eighteen mayor cancers in 1985. Int. J. Cancer 54: 594 - 606.

PREMPRO™ (conjugated estrogens/medroxyprogesterone acetate tablets) Brief Summary

(For Full Prescribing Information and Patient Information, See Package Circulars.)

Description: PREMPRO™ (conjugated estrogens/medroxyprogesterone acetate tablets) therapy consists of a single tablet containing 0.625 mg of the conjugated estrogens found in Premarin®, and 2.5 mg of medroxyprogesterone acetate (MPA), for oral administration.

ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA IN POSTMENOPAUSAL WOMEN. THIS FINDING REFERS TO ESTROGENS GIVEN WITHOUT PROGESTIN.

Progestins taken with estrogen drugs significantly reduce but do not eliminate this risk. Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

ESTROGENS/PROGESTINS SHOULD NOT BE USED DURING PREGNANCY.

There is no indication for estrogen therapy during pregnancy or during the immediate postpartum period. Estrogen therapy during pregnancy is associated with an increased risk of congenital defects in the reproductive organs of the fetus, and possibly other birth defects. Estrogens are not indicated for the prevention of postpartum breast engorgement.

Studies of women who received diethylstilbestrol (DES) during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life. The 1985 DES Task Force concluded that use of DES during pregnancy is associated with subsequent increased risk of breast cancer in the mothers, although a causal relationship remains unproven and the observed level of excess risk is similar to that for a number of other breast cancer risk factors.

Several reports also suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias, 5 to 8 per 1000 male births in the general population, may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risk to exposed female fetuses; some of these drugs induce mild virilization of the external genitalia of the female fetus. If the patient is exposed to PREMPRO™ (conjugated estrogens/medroxyprogesterone acetate) during pregnancy, or if she becomes pregnant while taking these drugs, she should be apprised of the potential risks to the fetus.

Estrogens are ineffective for the prevention or treatment of threatened or habitual abortion. There is no adequate evidence that progestational agents are effective in preventing habitual abortion when such drugs are given during the first trimester of pregnancy. Furthermore, in the vast majority of women, the cause of abortion is a defective ovum, which progestational agents could not be expected to influence. In addition, the use of progestational agents with their uterine-relaxant properties, in patients with fertilized defective ova, may cause a delay in spontaneous abortion.

Indications and Usage: Indicated in women with an intact uterus for the treatment of moderate to severe vasomotor symptoms associated with the menopause; treatment of vulvar and vaginal atrophy; prevention of osteoporosis (since estrogen administration is associated with risks as well as benefits, patient selection ideally should be based on prospective identification of risk factors for developing osteoporosis).

Contraindications: 1) Known or suspected pregnancy, including use for missed abortion or as a diagnostic test for pregnancy (see Boxed Warning). Estrogen or progestin may cause fetal harm when administered to a pregnant woman. 2) Known or suspected cancer of the breast. 3) Known or suspected estrogen-dependent neoplasia. 4) Undiagnosed abnormal genital bleeding. 5) Active or past history of thrombophlebitis, thromboembolic disorders, or stroke. 6) Liver dysfunction or disease.

PREMPRO should not be used in patients hypersensitive to its ingredients.

Warnings: ALL WARNINGS BELOW PERTAIN TO THE USE OF THIS COMBINATION PRODUCT. (Based on experience with estrogens and/or progestins):

Induction of malignant neoplasms

Breast cancer. Some studies have reported a moderately increased risk of breast cancer (relative risk of 1.3 to 2.0) in those women on estrogen replacement therapy (ERT) taking higher doses, or in those taking lower doses for prolonged periods of time, especially >10 years. The majority of studies, however, have not shown an association in women who have ever used ERT. The effect of added progestins on the risk of breast cancer is unknown, although a moderately increased risk in those taking combination estrogen/progestin therapy has been reported. Other studies have not shown this relationship.

Endometrial cancer. The reported endometrial cancer risk among users of unopposed estrogen was about 2- to 12-fold or greater than in nonusers and appears dependent on treatment duration and estrogen dose. There is no significant increased risk associated with estrogen use for <1 year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for 5 years or more. In one study, persistence of risk was demonstrated for 10 years after cessation of estrogen treatment. In another study, a significant decrease in the incidence of endometrial cancer occurred 6 months after estrogen withdrawal.

A large clinical trial demonstrated that MPA administered with Premarin markedly reduces the incidence of endometrial hyperplasia, a possible precursor of endometrial cancer. Endometrial hyperplasia has been reported in a large clinical trial to occur at a rate of approximately 1% or less with PREMPRO. Studies have also demonstrated a reduced risk of endometrial cancer when a progestin is given with ERT.

Clinical surveillance of all women taking estrogen/progestin combinations is important. Adequate diagnostic measures should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

Thromboembolic disorders and other vascular problems. In some epidemiological studies, women on estrogen replacement therapy, given alone or in combination with a progestin, have been reported to have an increased risk of thrombophlebitis, and/or thromboembolic disease, although the evidence is conflicting. The physician should be aware of the possibility of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism, and pulmonary embolism) during hormone replacement therapy and be alert to their earliest manifestations. Should any of these occur or be suspected, hormone replacement therapy should be discontinued immediately. Women who have risk factors for thrombotic disorders should be kept under careful observation.

Effects during pregnancy. Use in pregnancy is not recommended. See Boxed Warning.

Gallbladder disease. Two studies have reported a 2- to 4-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.

Elevated blood pressure. Occasional blood pressure increases during ERT have been attributed to idiosyncratic reactions to estrogens. More often, blood pressure has remained the same or has dropped. Postmenopausal estrogen use does not increase the risk of stroke. Nonetheless, blood pressure should be monitored at regular intervals with estrogen use.

Hypercalcemia. Estrogen therapy may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

Visual abnormalities. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. Withdraw medication if papilledema or retinal vascular lesions occur.

Precautions: GENERAL

Based on experience with estrogens and/or progestins:

Cardiovascular Risk. A causal relationship between ERT and reduction of cardiovascular disease in postmenopausal women has not been proven. The effect of added progestins on this putative benefit is not yet known.

Many published studies suggest that there may be a cause-effect relationship between postmenopausal oral ERT *without added progestins* and a decrease in cardiovascular disease. Although most of the observational studies which assessed this statistical association have reported a 20% to 50% reduction in coronary heart disease risk and associated mortality in estrogen takers, the following should be considered when interpreting these reports: Because only one of these studies was randomized and it was too small to yield statistically significant results, all relevant studies were subject to selection bias. Thus, the apparently reduced risk of coronary artery disease cannot be attributed with certainty to ERT. It may instead have been caused by life-style and medical characteristics of the women studied with the result that healthier women were selected for estrogen therapy. Ongoing and future large-scale randomized trials may fail to confirm this apparent benefit.

Current medical practice often includes the use of concomitant progestin therapy in women with intact uteri. While the effects of added progestins on the risk of ischemic heart disease are not known, MPA at the dose in PREMPRO™ (conjugated estrogens/medroxyprogesterone acetate tablets) attenuates much of the favorable effect of conjugated estrogens on HDL levels, although it maintains the favorable effect of conjugated estrogens on LDL levels (see **Clinical Pharmacology** in Full Prescribing Information).

The effects of added progestins on the risk of breast cancer are also unknown, however, available epidemiologic evidence suggests that progestins may enhance the moderately increased breast cancer risk reported with prolonged ERT (see **Warnings** section).

The safety data regarding PREMPRO were obtained primarily from clinical trials and epidemiologic studies of postmenopausal Caucasian women, who were at generally low risk for cardiovascular disease and higher than average risk for osteoporosis. The safety profile of PREMPRO derived from these study populations cannot necessarily be extrapolated to other populations of diverse racial and/or demographic composition. When considering prescribing PREMPRO, physicians are advised to weigh the potential benefits and risks of therapy as applicable to each individual patient.

Use in hysterectomized women. Data do not support the use of combined estrogen/progestin in postmenopausal women without a uterus; possible risks may be associated with this combined regimen. Potential risks include some deterioration in glucose tolerance and less favorable effects on lipid metabolism as compared to lipid effects of Premarin® (conjugated estrogens tablets, USP) alone.

Physical examination. A complete medical and family history should be taken prior to the initiation of therapy with special reference to blood pressure, breast, abdomen, and pelvic organs, as well as a Papanicolaou smear. Generally, estrogen should not be prescribed for longer than one year without another physical examination being performed.

Fluid retention. Conditions influenced by fluid retention, such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.

Uterine bleeding. Certain patients may develop abnormal uterine bleeding; if undiagnosed, adequate diagnostic measures are indicated. (See **Warnings**.)

Advise pathologist of estrogen/progestin therapy when relevant specimens are submitted.

Based on experience with estrogens:

Familial hyperlipoproteinemia. Estrogen therapy may be associated with massive elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects of lipoprotein metabolism.

Hypercoagulability. Women taking ERT may have hypercoagulability primarily related to decreased antithrombin activity. This appears dose- and duration-dependent and is less pronounced than that associated with oral contraceptive use. Also, postmenopausal women tend to have changes in levels of coagulation parameters at baseline compared to premenopausal women. There is insufficient information on hypercoagulability in women who have had previous thromboembolic disease.

Mastodynia. Certain patients may develop this undesirable manifestation of estrogenic stimulation.

Based on experience with progestins:

Lipoprotein metabolism. See **Clinical Pharmacology** in Full Prescribing Information.

Impaired glucose tolerance. See *Use in hysterectomized women,* above.

Depression. Observe patients who have a history of depression and discontinue the drugs if depression recurs to a serious degree.

DRUG/LABORATORY TEST INTERACTIONS—1) Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity. 2) Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. 3) Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin). 4) Increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglyceride levels. 5) Impaired glucose tolerance. Observe diabetic patients carefully. 6) Reduced response to metyrapone test. 7) Reduced serum folate concentration. 8) Aminoglutethimide administered concomitantly with MPA may significantly depress the bioavailability of MPA.

CARCINOGENESIS, MUTAGENESIS AND IMPAIRMENT OF FERTILITY. Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breasts, uterus, cervix, vagina, testis, and liver. (See **Contraindications** and **Warnings**.)

Female rats exposed to dietary dosages of up to 5000 μg/kg/day of MPA (50 times higher—based on AUC values—than the level observed experimentally in women taking 10 mg of MPA), exhibited a dose-related increase in pancreatic islet cell tumors (adenomas and carcinomas). Pancreatic tumor incidence was increased at 1000 and 5000 μg/kg/day, but not at 200 μg/kg/day.

A decreased incidence of spontaneous mammary gland tumors was observed in all three MPA-treated groups, compared to controls, in the two-year rat study. This decreased incidence may be linked to the significant decrease in serum prolactin concentration observed in rats.

Beagle dogs treated with MPA developed mammary nodules, some of which were malignant. Although nodules occasionally appeared in control animals, they were intermittent in nature, whereas the nodules in the drug-treated animals were larger, more numerous, persistent, and there were some breast malignancies with metastases. Progestogens stimulate synthesis and release of growth hormone (GH) in dogs, resulting in stimulation of mammary growth and tumors. In contrast, GH in humans is not increased, nor does GH have any significant mammotrophic role. Therefore, the MPA-induced increase of mammary tumors in dogs probably has no significance to humans. No pancreatic tumors occurred in dogs.

PREGNANCY CATEGORY X—Estrogens/progestins should not be used during pregnancy. See **Contraindications** and Boxed Warning.

NURSING MOTHERS—Generally, drugs should not be given to nursing mothers unless clearly necessary since many drugs are excreted in human milk. Estrogen administration to nursing mothers may decrease the milk's quantity and quality. Detectable amounts of progestin have been identified in the milk of mothers receiving the drug. The effect of this on the nursing infant is not known.

Adverse Reactions: (See **Warnings** regarding induction of neoplasia, adverse effects on the fetus, increased incidence of gallbladder disease, elevated blood pressure, thromboembolic disorders, cardiovascular disease, visual abnormalities, and hypercalcemia and **Precautions** for cardiovascular disease.)

The following adverse reactions have been reported with estrogen and/or progestin therapy: *Genitourinary system.* Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow, breakthrough bleeding, spotting, change in amount of cervical secretion, premenstrual-like syndrome, cystitis-like syndrome, increase in size of uterine leiomyomata, vaginal candidiasis, amenorrhea, changes in cervical erosion. *Breasts.* Tenderness, enlargement, galactorrhea. *Gastrointestinal.* Nausea, cholestatic jaundice, changes in appetite, vomiting, abdominal cramps, bloating, increased incidence of gallbladder disease, pancreatitis. *Skin.* Chloasma or melasma that may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism, itching, urticaria, pruritus, generalized rash, rash (allergic) with and without pruritus, acne. *Cardiovascular.* In susceptible individuals, change in blood pressure, thrombophlebitis, pulmonary embolism, cerebral thrombosis and embolism. *CNS.* Headache, dizziness, mental depression, nervousness, migraine, chorea, insomnia, somnolence. *Eyes.* Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis. Steepening of corneal curvature, intolerance of contact lenses. *Miscellaneous.* Increase or decrease in weight, edema, changes in libido, fatigue, backache, reduced carbohydrate tolerance, aggravation of porphyria, pyrexia, anaphylactoid reactions, anaphylaxis.

Acute Overdosage: May cause nausea and vomiting; withdrawal bleeding may occur in females.

Dosage and Administration: PREMPRO 0.625 mg/2.5 mg therapy consists of a single tablet to be taken once daily.

For moderate to severe vasomotor symptoms, vulvar and vaginal atrophy—reevaluate patients at 3-month to 6-month intervals to determine if treatment is still necessary.

For prevention of osteoporosis—monitor patients closely for signs of endometrial cancer; appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

This brief summary is based on PREMPRO CI4664-3, Revised 5/21/97.

Reference: 1. Data on file, Wyeth-Ayerst Laboratories. PREMARIN® (conjugated estrogens tablets, USP) Prescribing Information.

After 55 years, we're discover

That's



ing more.

why Nothing Else Is Premarin.™

PREMARIN is grounded in 5 decades of experience, and has been used by tens of millions of women. Initially, PREMARIN was prescribed to dramatically reduce the troublesome symptoms of menopause, helping women feel better and enjoy life. Through the years, researchers began to ask questions about the role of PREMARIN in many diseases affecting menopausal women. These questions initially led us to recognize the role of PREMARIN in the prevention and management of osteoporosis, including the reduction of fracture risk.[1]

Now, the PREMARIN family of products is the hormone replacement therapy being used in several large-scale studies on the consequences of menopause, including the well-publicized Women's Health Initiative trials.

PREMARIN: You knew it was right for her when she entered menopause, to help her feel like herself again. Now, we are discovering the true potential of PREMARIN throughout every phase of her menopause—from hot flashes and vaginal changes to fracture prevention—and beyond.

PREMARIN is indicated for the prevention and management of osteoporosis and the treatment of moderate to severe vasomotor symptoms associated with menopause.

Contraindications: *Estrogens should not be used in women (or men) with any of the following conditions:* ***1)*** *known or suspected pregnancy,* ***2)*** *known or suspected breast cancer,* ***3)*** *known or suspected estrogen-dependent neoplasia,* ***4)*** *undiagnosed abnormal genital bleeding,* ***5)*** *active thrombophlebitis or thromboembolic disorders.*

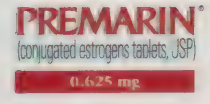
PREMARIN should not be used in patients hypersensitive to its ingredients.

Note: Estrogens have been reported to increase the risk of endometrial carcinoma in postmenopausal women. This finding refers to estrogens given without progestin.

Please see adjacent page for brief summary of Prescribing Information.

For my patients, it's

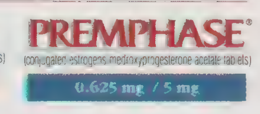
PREMARIN® (conjugated estrogens tablets, USP) ***Family of Products***



PREMARIN® 0.625 mg/g (conjugated estrogens) VAGINAL CREAM
in a nonliquefying base







PREMPRO™ 5 mg NOW AVAILABLE!

Vol. 90 • 7-8-9-10-11-12 / 1998 • Pág. 144, 153

Artículos Especiales:

El Fenómeno de la Violencia Contra los(as) Ancianos(as) Puertorriqueños(as)

Por: José R. Rodríguez, MD, MPH, Ph.D*
Gladys Altieri, Ph.D.**

Abstract: *The present study is the first one to our knowledge that tries to give a panoramic view and explore the problem of Elderly Abuse in Puerto Rico. A retrospective statistical analysis of frequencies of cases by sex gender, age strata and region has been obtained showing an increasing tendency of cases.*

We conclude that the phenomena of abuse in the Puerto Rican Elderly population is one that requires rapid interventions with emphasis in the prevention component.

INTRODUCCION:

El fenómeno de la violencia contra el(la) anciano(a) puertorriqueño(a) y sus múltiples formas de expresión como son el maltrato, abuso, explotación e insultos, entre otras, es uno sumamente complejo. Durante la última década, se ha intentado crear conciencia del maltrato de los(as) ancianos(as) en el ambiente del hogar. La violencia o maltrato en contra del(la) anciano(a) en el hogar no ha recibido la misma atención que la violencia conyugal o el maltrato de menores. Cuando se menciona maltrato o negligencia entre los(as) ancianos(as), se piensa en aquellos que están en asilos, o en aquellos que son asaltados en la calle o son víctimas de fraudes o timos económicos. Se han tomado medidas remediativas como son las leyes para la protección de los(as) ancianos(as), la educación de profesionales en campos relacionados, hasta la convicción de los victimarios. A pesar de estos esfuerzos, el maltrato de los(as) ancianos(as) continúa siendo un secreto que se esconde en las familias.

El siguiente artículo pretende proveer una visión integral sobre el tema presentando los tipos de maltrato más comunes contra el(la) anciano(a) discutiendo sus implicaciones a nivel social.

Fenomenología Socio-Demográfica de la Población de Ancianos(as) en Puerto Rico. Se presenta una descripción socio-demográfica de la población de ancianos(as) puertorriqueños(as) con la finalidad de familiarizar al lector con ésta. La población de ancianos(as) ha ido en aumento a través de los años respondiendo a cambios en variables demográficas como son la natalidad, migración, y mortalidad.[1]

Para 1990 Puerto Rico contaba con una población total aproximada de 3,522,O37 habitantes, de los cuales 340,884 eran ciudadanos de 65 años o más, representando esto el 9.7% de la población total. Si se reduce la edad de referencia a 60 años, para el 1990 se tenía 465,736,1o que representa un 13.2% de la población puertorriqueña. [2-3] Los demógrafos señalan que cualquier población que esté o sobrepase el 10% de personas de 65 años o más puede ser considerada como una población envejecida. Puerto Rico, de continuar el ritmo de crecimiento poblacional que tiene en estos momentos, tendrá, según estimados de la Junta de Planificación de P.R., una población para el año 2000 de 575, 329 ancianos(as) representando un 15.2% de la población total de la Isla.

Algunas características particulares de la población de ancianos(as) son:

a. La mayor proporción de personas de edad avanzada se encuentra en el grupo de edad de 60-69 años, aproximadamente un 51%.

b. De la población de 60 años o más la mayor parte pertenece al sexo femenino. De hecho, existen aproximadamente 117 mujeres, por cada 100 hombres, en este grupo de edad.

c. La población de ancianos(as) se concentra en mayor proporción en la zona urbana.

d. Mueren usualmente del corazón o de tumores malignos.

e. Viven en lo que se denomina hogares de familia común, ésto es, unidades familiares en las que

*Catedrático Asociado Centro Caribeño de Estudios Postgraduado y Programa de Gerontología, RCM
**Directora Programa Psy.D. - Centro Caribeño de Estudios Postgraduados
Agradecemos la ayuda suministrada por la Oficina del Gobernador para Asuntos de la Vejez de P.R., especialmente a la Lcda. Ruby Rodríguez, Directora Ejecutiva, Srta. Nellie Pagán y Sra. Damaris Vera de la Sección de Planificación. De igual forma agradecemos la labor secretarial de la Sra. Aida Ayende.

habitan dos o más personas relacionadas entre sí por lazos de sangre, adopción o matrimonio.

f. Sólo menos de un 1.5% viven en lo que se denomina alojamientos de grupo.

g. Más de la mitad de esta población se encuentra bajo el nivel de pobreza (56%).

h. Las tasas de actividad económica para la población de 65 años o más son las más bajas desde los 1940 hasta el 1990. Esto significa que un número mínimo de personas ancianas se encuentra empleado o buscando trabajo, aumentando así su problema de pobreza.

i. Usualmente aquéllos que padecen de enfermedades son enfermedades crónicas (i.e., diabetes, hipertensión y osteoartritis)

Debe comenzarse a tener conciencia de que es una población que comienza a ser numerosa, la cual presentará una avalancha de problemas serios, según la descripción que se ha presentado. Será necesario aprestarnos a trabajar de una manera más diligente para ser efectivos. Existen programas comunitarios, aunque tal vez no los suficientes. Se tiene que comenzar a aumentar los programas comunitarios que sirven esta población. La realidad es que no se ha estado haciendo con la suficiente rapidez, resultando en la posibilidad de tener más ancianos(as) a riesgo de ser maltratados.

EL MALTRATO COMO UNA EXPRESION DE LA VIOLENCIA CONTRA EL ANCIANO(A) PUERTORRIQUEÑO(A) ALGUNOS DILEMAS EN LAS DEFINICIONES OPERACIONALES

Los avances socio-económicos en Puerto Rico han traído cambios drásticos en todos los aspectos de nuestra vida. Avances en la medicina preventiva como curativa, mejor nutrición y estilos de vida han hecho que la expectativa de vida del puertorriqueño aumente hoy día hasta los 81 años. De los problemas sociales de mayor impacto en P.R. en los últimos años, el de maltrato y violencia doméstica, han sido de los más severos por las repercusiones tan serias que conllevan. Específicamente, el maltrato hacia los(as) ancianos(as) es un problema social de grandes dimensiones al cual desafortunadamente se le ha prestado poca atención. Siendo los(as) ancianos(as) un grupo poblacional de por sí frágil, y veremos dentro de breve los porqué, es necesario intervenir lo antes posible, o mejor prevenir la situación de maltrato o abuso, como expresiones comunes de la violencia contra el(la) anciano(a). En este artículo se hará énfasis en el fenómeno del maltrato o abuso como expresiones cotidianas del fenómeno de la violencia contra el(la) anciano(a) puertorriqueño(a).

Aún cuando el maltrato en los(as) ancianos(as) es algo que ha existido en todas las épocas, se entiende que el interés en el tema se inicia a partir de las investigaciones en violencia doméstica en los años 60 lo cual llevó al descubrimiento de un número significativo de ancianos(as) maltratados(as). De hecho, no es hasta hace 20 años aproximadamente que aparecen sistemáticamente reportados los primeros casos de abuso contra ancianos(as) en la literatura científica.[4] Investigadores como Ramos (1991) señalan que la primera referencia en la literatura sobre el maltrato en el(la) anciano(a) lo fue una carta escrita por Burston en el 1975, dirigida al editor de la publicación British Medical Journal, titulada "Granny Battering".[5]

El problema tiene tan serias implicaciones que en 1991 un informe auspiciado por el Congreso de los Estados Unidos señala que aproximadamente entre 1 a 2 millones de ancianos(as) son víctimas de maltrato. Estudios más recientes sugieren que la prevalencia de maltrato en los(as) ancianos(as) estadounidenses es de aproximadamente un 4% de la población total.[6]

Aún cuando múltiples investigadores han tratado de determinar la amplitud y prevalencia del problema, al haber éstos operacionalizado de diferente manera la variable maltrato/abuso en sus estudios, han creado un problema conceptual de cuál definición utilizar para esclarecer de forma fehaciente lo que es el fenómeno de maltrato o abuso hacia el anciano(a).[7-8-9] Luego de revisar la literatura gerontológica, Rodríguez[20] sugiere la siguiente definición:

"La violencia, manifestada a través del abuso/maltrato, contra un ser humano puede ser descrita como una de carácter físico, sexual, psicológico/emocional, financiero o legal. Puede ser autoinfligido o infligido por una o varias personas que tengan poder sobre el(la) anciano(a). Puede ser intencional o no, activo o pasivo, o ser el resultado de la ignorancia, negligencia u omisión por parte de la persona que lo/la cuide. Causa un determinado daño al anciano(a), a veces de carácter irreversible."

Algunos investigadores han señalado el cuidado que hay que tener al utilizar una única definición por la posible restricción que se haga al definir el fenómeno, limitando o excluyendo, algunas facetas del evento que puedan ser importantes.[10]

Se reconoce que aún cuando una definición única puede ser cuestionable, el hecho es que requerimos de una, para tener un marco directivo en el cual basar nuestras investigaciones y trabajos de forma práctica. De otra manera, nos seria imposible operacionalizar y establecer quién es maltratrado, abusado o víctima de algún tipo de violencia y quién no lo es.

FACTORES DE RIESGO:

La literatura señala que existe un ámbito multifactorial e interdisciplinario cuando se trata de identificar aquellos factores de riesgos relacionados al maltrato para poder confirmar aquellos indicadores de maltrato/violencia contra el(la) anciano(a) en más de una dirección. Algunos investigadores plantean una serie de factores que dificulta la identificación del abuso en el(la) anciano(a).[5-6-11] El primero es la falta de consenso en lo que se define como maltrato hacia el(la) anciano(a), lo cual hace dificil el que pueda detectarse y denunciarse. El segundo es la marginación en la que muchos de los(as) ancianos(as) se encuentran de sus redes de apoyo. Su propia condición de anciano(a) hace más fácil que se aísle socialmente debido, entre otros, a que han muerto las personas con quienes compartían o porque no le es fácil llegar a los sitios de confraternización o reunión. Este aislamiento se hace mayor cuando existen problemas de salud y es aquí cuando a mayor riesgo puede estar el(la) anciano(a), pues la tensión familiar o institucional, a su vez se hace mayor por las demandas de cuidados que requiere el(la) anciano(a)[12]

De todas formas, la literatura ha sido consistente al generar una lista de condiciones o factores que contribuyen al maltrato/abuso del anciano(a). Resumidas como:

1. Un aumento en la condición de dependencia. Según el(la) anciano(a) se vuelve más dependiente, esto genera una mayor ansiedad por parte de los que lo cuidan. La contraparte también es cierta, familiares que sean excesivamente dependientes de un(a) anciano(a) (financieramente o por necesidad de albergue) pueden estar a riesgo de que maltraten al anciano(a). Tambien familiares con problemas de abuso de drogas o problemas mentales pueden ser más propensos a maltratar.

2. Múltiple dependencia. No es raro por parte del que cuida al anciano(a), una sobrecarga de responsabilidades lo que hace que, por ejemplo, una madre que tenga hijos pequeños se vea exhausta o una esposa también anciana se agote.

3. Historial previo de relaciones interfamiliares pobres o negativas.

4. Historial previo de abuso o maltrato en la familia, por ejemplo, abuso físico o sexual de los niños o violencia marital.

5. Que se tenga en la familia algún historial previo de problemas psiquiátricos o psicológicos.

6. El(la) anciano(a) puede presentar condiciones de salud específicas que requieran un cuidado más especializado lo cual aumenta la tensión en la persona a cargo.

7. Problemas del medio ambiente. Una familia que viva con un(a) anciano(a) en un área de gran pobreza o en una estructura física que se encuentre "sobrepoblada" y maltrecha, puede ocasionar niveles de tensión o ansiedad insoportables haciendo más fácil el que se pueda generar el abuso o maltrato al anciano(a).

8. Problemas financieros en la familia. Una persona dependiente puede ser una carga financiera para quienes lo cuidan, sobre todo, si éstos no conocen aquellos beneficios que pueden solicitar o aquellos servicios a que tienen derecho.

9. En términos de la persona que lo cuida, ésta puede tener a su vez problemas de salud, financieros, interpersonales o de cualquier otra índole por lo cual hace más dificil la situación de cuido.

10. Inadecuacidad del sistema. Se refiere a la poca ayuda de las instituciones formales (iglesias, agencias privadas, agencias del gobierno etc.) que puedan proveer para el(la) anciano(a) o quienes lo cuidan. No son pocas las agencias con presupuestos limitados las cuales tienen dificultades en proveer adiestramientos necesarios para orientar a los asistentes en las necesidades y los métodos del trato hacia personas mayores abusadas o abandonadas o proveer ayuda directa. Puerto Rico no es la excepción en la limitación de recursos financieros gubernamentales o privados. La ineficiencia del sistema puede ser considerado un tipo de maltrato al no presentar recursos necesarios para satisfacer las demandas válidas requeridas por el(la) anciano(a) o por hacer caso omiso a las mismas.

En ocasiones, el(la) mismo anciano(a) sin saberlo crea una situación de alto riesgo tentando a sus herederos con dinero o posiciones mediante regalos o a través de un testamento. Los(as) ancianos(as) pueden amenazar con cambiar el testamento dependiendo del comportamiento o la atención que reciba de sus herederos . En términos generales, todos estos factores de riesgo deben verse en forma integral, reconociendo que pueden darse al unísono o individualmente. El reconocerlos rápidamente permite trabajar más efectivamente con ellos.

TIPOS DE ABUSO CONTRA EL(LA) ANCIANO(A):

Se describe a continuación los tipos más comunes de abuso o maltrato en el(la) anciano(a) haciendo énfasis en que dichos tipos no son exclusivos de esta población.

La victimización del anciano(a) se percibe como una muy atractiva ya que se visualiza a éste como una persona vulnerable como víctima.s Para el perpetrador, el(la) anciano(a) es una víctima que ofrece mayores oportunidades de obtener beneficios con unos riesgos mínimos.

Es importante señalar que la amplia gama de tipos de maltrato, su severidad y la poca visibilidad pública, han hecho dificil el estimar el número total de maltrato, por lo que al presente no se tiene, con la excepción de los limitados informes de la Oficina de Asuntos de la Vejez: Oficina del Gobernador de P.R., ningún censo de prevalencia longitudinal. Estos datos serán presentados más adelante cuando se discuta el caso de Puerto Rico en detalle.

Los tipos de abusos o maltratos que la literatura más reciente señala con relación al anciano(a). Estos son:

A. *maltrato fisíco contra el(la) anciano(a):*

Incluye cualquier acción donde exista violencia o maltrato físico significando ésto la capacidad de infligir dolor o daño. Los actos violentos comunes contra el(la) anciano(a) incluyen, pero no se limitan a abofetearlo, jamaquearlo, empujarlo, apretarlo con coraje o tirarle con objetos. Lo anterior tiene como resultado la posibilidad de crearles fracturas óseas o laceraciones. Los(as) ancianos(as) tienen una gran posibilidad de sufrir de osteoporosis y otros problemas mio-osteo-artríticos, además de la fragilidad de la piel por su edad, por lo que lo hacen aún más sensitivos a dichos actos. Privar al anciano(a) de ayudas tales como espejuelos, audífonos o un andador, también es considerado maltrato.

B. *maltrato psicológico contra el anciano(a):*

Usualmente reconocido como un acto que tiene la intención de causar angustia mental o degradación del "yo". Ejemplos más comunes lo son poner sobre-nombres, amenazarlos, asustarlos, tratarlos como niños, insultarlos, ingnorarlos o humillarlos. El abandono institucionalizado, aunque puede ser categorizado como un área exclusiva, puede ser también fácilmente incluido como una forma de maltrato psicológico.

C. *maltrato económico-legal:*

Este tipo de maltrato ha sido subdividido en tres categorías básicas. La primera de ella es la explotación material, en la cual el custodio del(la) anciano(a) hace mal uso de las propiedades, posesiones, dinero o seguros de vida del (la)anciano(a). En términos generales, no se le permite el disfrute pleno de aquellos bienes gananciales/materiales o hace que éstos sean inaccesibles. La segunda categoría es la apropiación ilegal o robo. En esta se priva al anciano(a) de su dinero, posesiones o propiedades a través de engaños o estafa o se le estorciona para accesar sus ahorros o bienes. La tercera categoría es la explotación, donde el custodio le puede negar sus derechos, lo puede obligar a realizar tareas en contra de su voluntad o a realizar tareas incompatibles con su capacidad física.

D. *maltrato sociológico:*

Interesantemente este tipo de maltrato puede considerarse bastante prevalente. Se refiere al aislamiento, apartar el(la) anciano(a) de su red de apoyo o de sus roles tradicionales (sin pensar en elementos adaptativos para éste) u obligarlos a estar en actividades o sitios que él no desea. Es aquí donde el(la) anciano(a) pierde autonomía e independencia provocando ésto una confusión de roles. Usualmente se le dirige a que se acople a nuevos horarios y actividades sin tomar en consideración los horarios o actividades que el(la) anciano(a) no puede o no desea seguir.

E. *maltrato/abuso sexual:*

Este tipo de maltrato puede tener varias pendientes. Una de las facetas puede ser el abuso sexual que alguien pueda tener de un(a) anciano(a). Otras veces puede responder a la estigmatización negativa que tenemos del(la)anciano(a) en cuanto a su viabilidad y deseos de mantener actividad sexual o la invasión a la privacidad.[13] Debido a que dicha área se ha mantenido como un "tabú", sobre todo en el hogar y la Iglesia, hay que empezar a explorar posibles formas de cómo lidiar con la situación. De hecho, aún cuando existen algunos estudios que encuentran que 88% de las víctimas de abuso sexual eran ancianas, de las cuales, la mayoría se encontraban desorientadas o habían sufrido un accidente cerebrovascular, es esta área una que requiere de mayor investigación por el desconocimiento manifiesto que se tiene al presente [11-12-14]

F. *abandono*

Se refiere a la inhabilidad o falta del proveedor de servicios (sea éste una agencia, institución o persona) de satisfacer las necesidades vitales del(la) anciano(a) dependiente. Ejemplo de ésto puede ser ignorar al anciano, abandonarlo a su suerte en algún auspicio o asilo, o no proveerle sus medicamentos, o sencillamente una inhabilidad o imposibilidad genuina de suministrar el servicio o cuido necesario. El aislamiento se puede hacer mayor cuando hay problemas de salud haciendo más prevalente en esta situación este tipo de maltrato.

Se debe recordar que la detección del maltrato está impedida muchas veces por la renuencia del anciano(a) de informarlo. Interesantemente, en una encuesta realizada en Estados Unidos se encontró que sólo el 24% de los casos conocidos de maltrato fueron informados por las víctimas y que el 36% de

las víctimas no aceptaban este problema.[6] Las razones que se presentan para esta renuencia son múltiples, entre otras, el que normalmente la víctima depende del perpetrador para su supervivencia básica y teme a las represalias o a que la situación empeore. El(la) anciano(a) puede sentir temor a ser removido del hogar y ser institucionalizado. Tambien existe la preocupación de afectar no sólo su estatus social sino el de su familia si los denuncian. Hay que recordar que, en términos generales, los(as) ancianos(as) están socializados fuertemente a que los eventos de la familia son privados. Su alto sentido de honestidad y lealtad hacia su familia hace difícil que denuncien el maltrato del que pueden ser víctimas.

Estas son variables que se tienen que empezar a comprender y a trabajar si queremos ser efectivos tanto en la prevención como el manejo del problema.

COMO RECONOCER AL ANCIANO(A) MALTRATADO(A):

El reconocer a un(a) anciano(a) maltratado(a) no es tarea fácil, sobre todo por los "clichés" o estereotipos asociados a los ancianos(as). Por ejemplo, se acepta muy rápidamente, "el que son frágiles y débiles y tienden a tener accidentes muy fácilmente por sus limitaciones físicas". Ser un poco más suspicaces, y aún cuando lo más obvio es buscar signos físicos de maltrato, no se debe limitar a éstos.

Se debe recordar que no pocos golpes pueden ser dados en áreas corporales no visibles, además de que probar determinadas lesiones como no accidentales puede ser una labor titánica.

De allí que se tenga que comenzar a reflexionar sobre aquellas señales que se deben buscar. Ejemplo de estas son:

1. En términos de daño físico:
   - hematomas sobre todo en áreas no visibles o cubiertas
   - fracturas continuas
   - quemaduras
   - laceraciones por abrasión o presión indebida, sobre todo en extremidades
   - cortaduras

2. En términos de abandono:
   - falta de higiene, ej. olor a sudor, heces fecales u orina
   - pérdida de peso sin razón aparente
   - aislamiento social
   - mobilidad restringida sin causa aparente o por falta de ayuda

3. En términos de abuso sexual:
   - irritación urinaria o problemas genito-urinarios
   - infecciones frecuentes del tracto genito-urinario
   - sangramiento o descarga vaginal o anal
   - cortaduras o laceraciones vaginales o anales
   - enfermedades de transmisión sexual
   - súbita confusión
   - depresión
   - agitación severa, temor o tristeza al vestirse, desvestirse, bañarse o ser examinado(a) por un médico
   - imposibilidad de obtener un lugar adecuado para su expresión sexual.
   - timidez a ser ridiculizado(a) cuando se habla de temas sexuales

4. En términos de maltrato económico:
   - estar pendiente de expresiones como ". . .no puedo comprar tal o cual cosa", "el dinero se lo gasta mi hijo/a", "...no sé cuándo me llega el seguro social, o el dinero de la pensión o rentas"
   - a manipulación de testamentos, declarándosele "incompetente" por alguien sin autoridad
   - las facturas no se pagan o se comienzan a pagar tardíamente cuando se supone que alguien las esté pagando
   - el(la) anciano(a) toma préstamos grandes sin razón aparente el(la) anciano(a) transfiere el título de sus propiedades, hogar u otros bienes sin razón aparente.
   - se informa de actividad inusual o inapropiada en su cuenta de banco u otros bienes asociados.
   - se entregan demasiados cheques para cambiar en efectivo a un encargado de la salud, profesional o familiar sin razón aparente.

El reconocer un(a) anciano(a) víctima de maltrato no es tarea simple. Muchas víctimas pasan desapercibidas a través del tiempo y no es hasta muy tarde, que quizás puedan ser reconocidas. Se debe comenzar a adiestrar para lograr esta tarea, la cual repercutirá en beneficio de la población gerontológica.

COMO TRABAJAR CON EL ANCIANO(A) MALTRATADO(A):

En primera instancia hay que reconocer que el problema tiene dos caras, el(la) anciano(a) maltratado(a) y quién lo maltrata que frecuentemente es un familiar muy cercano. Si bien es cierto que la seguridad del(la) anciano(a) es vital, también se debe reconocer que quien lo maltrata puede tener un sinnúmero de problemas muy serios y necesitar, de igual forma que el(la) anciano(a), de ayuda inmediata. Varios estudiosos opinan que el historial obtenido mediante una simple entrevista individual, tanto al anciano(a) como al presunto maltratante, es el inicio del poder identificar problemas de abuso y posibles referidos para poder ayudarles. [15-16]

Según Pritchard (1995), existen dos reglas simples para trabajar con el(la) anciano(a) maltratado(a), estas son:[15]

1. Escuche al anciano(a) realmente. Es fácil hacer caso omiso a los comentarios de un(a) anciano(a) por asumirse que éste está fuera de sus cabales, confundido o por padecer de alguna enfermedad mental. Si bien es cierto que no se puede descartar lo anterior, es recomendable y juicioso indagar un poco más allá de lo que se escucha pua explorar la veracidad de lo que el(la) anciano(a) ha verbalizado.

2. No ignore la queja o acusación de abuso o maltrato. Es muy fácil ignorar una acusación de maltrato especialmente cuando la víctima rechaza el que esté siendo maltratada o se niega a recibir ayuda. Se debe reconocer dichas situaciones y tratar de proveer asistencia inmediata, aún informar al anciano(a) de la existencia de aquellas agencias que le puedan proveer ayuda, además de hacerle conocer que no se encuentra solo(a) y que la ley lo ampara. De igual forma es vital el que reconozca que tiene a alguien en quien confiar, explicándole cuáles son sus alternativas viables.

Pueden existir problemas de comprensión de parte del(la) anciano(a), especialmente, si éste tiene limitaciones mentales o físicas severas. Sin embargo, se debe reconocer que existen alternativas (i.e., legales, sociales) para manejar aquellos problemas difíciles. Lo importante es el interés que se tome en tratar de resolver o intervenir con la situación.

Los profesionales en el área de maltrato al anciano(a), frecuentemente sienten frustración y decepción al intentar desarrollar estrategias de ayuda para víctimas que rehúsan ser ayudados y para victimarios que niegan el abuso al(la) anciano(a). Por éste y otros motivos, los teorizantes[6,20] focalizan sus técnicas en estrategias a corto plazo, supervisión o monitoreo constante e intervenciones colaborativas con otros profesionales, familiares, amigos y miembros de la comunidad.

En el tratamiento a corto plazo, se abandona el concepto de "curación". El profesional debe aceptar el hecho de que las metas terapéuticas son limitadas, especialmente en aquellos casos donde existen problemas múltiples y difíciles de resolver en corto tiempo. El tratamiento breve está dirigido a la solución inmediata de los problemas que enfrenta el anciano(a) al momento y la restauración y realce del funcionamiento adaptativo del anciano(a). Hace énfasis también en eliminar o reducir síntomas específicos lo más posible.

El profesional debe ser visto como la persona agradable y sincera en quien se puede confiar. Algunos de los procedimientos utilizados en las intervenciones breves con ancianos(as) maltratados son; auscultar su realidad, intelectualización, seguridad y apoyo y el aumento y fortalecimiento de la autoestima del anciano(a). Las metas deben ser concretas y específicas. El uso de referidos a otros servicios y agencias de la comunidad es una estrategia valiosa, ya que provee toda una red de agencias de comunidad y de ayuda interdisciplinaria. Las metas son, en gran medida, determinadas por lo que el profesional considere que sería"el próximo paso más beneficioso".[6-11-17]

En el tratamiento breve se hace menos énfasis en el desarrollo de una relación terapéutica, ya que el profesional se mantiene involucrado con el(la) anciano(a) hasta tanto se desarrollen planes adecuados para un cuido prolongado de calidad y el monitoreo del mismo. Se sugiere que el centro de la intervención debe ser el motivar al anciano(a) a buscar alivio a su malestar y no el promover cambios permanentes en el comportamiento.[12-16-18]

En la mayoría de los casos de maltrato de ancianos(as), encontramos una víctima que escoge permanecer en la relación abusiva por el temor a tener que marcharse a un asilo por la separación física de su victimario. Es por ésto que se recomienda atender las necesidades de ambas personas. El profesional se convierte entonces, en un defensor del anciano(a) y un supervisor-amonestador del victimario. La meta de este tipo de intervención es eliminar el maltrato. Está basada en la teoría de aprendizaje social la cual establece que la conducta es aprendida de nuestra familia de origen, la cultura y las experiencias previas. Por lo tanto, si estos comportamientos son aprendidos, pueden ser desaprendidos y reemplazados por alternativas aceptables a todos.

La literatura reconoce estrategias específicas para la intervención con ancianos(as) maltratados(as):

- *Trabajar con la resistencia:*
  Resulta difícil aceptar que un(a) anciano(a) ofrezca resistencia a recibir ayuda para terminar con una situación de maltrato. Esta resistencia puede ser resultado de aislamiento o sentimientos de soledad, de la carencia de destrezas de manejo de los problemas del diario vivir y falta de conocimiento sobre cómo y dónde buscar ayuda. También puede ser resultado del temor el cual puede combatirse mediante la información y adiestramiento en el manejo de situaciones cotidianas que enfrenta el(la) anciano(a) en su diario vivir. El profesional debe validar el pesimismo y el temor que pueda sentir el(la) anciano(a) ante la posible resolución de sus problemas, con frases tales como, "Vamos a suponer que las cosas no se resolverán de inmediato y que no progresaremos muy rápido con su hijo". Esto lo enfrenta a una realidad genuina de su situación y a la vez trabaja con expectativas falsas que puedan aumentar la ansiedad y el desasosiego.

Tambien ayuda a aclarar que el "poco" progreso en la intervención no es responsabilidad exclusiva del anciano(a).

Cuando el(la) anciano(a) tiene pensamientos negativos y ansiedad, se recomienda ofrecer apoyo y explorar posibles fantasías, expectativas y temores en detalle. El(la) anciano(a) puede tener creencias equivocadas que deben ser combatidas, como por ejemplo, "Si las personas se enteran que mi hijo me pega, se preguntarán qué he hecho para merecerlo". El profesional debe asegurar al anciano que la culpa es una reacción común en esos casos y recalcar la necesidad de ayudar la familia para terminar con el maltrato. Es importante, además, ofrecer seguridad con frases tales como, "Debe sentirse orgullosa/o por ser tan valiente de aceptar la ayuda y trabajar por el bienestar de su familia".

- *Cortesía y respeto:*

El ser cortés y respetuoso contribuye a aumentar el deseo del anciano(a) de participar en el tratamiento. Existen unas reglas básicas que debemos seguir para demostrar nuestro respeto por el(la) anciano(a): debe informársele con anticipación si el profesional se va a ausentar a una visita. Un(a) anciano(a) puede pasar largas horas asomándose a la ventana para cotejar si llegó su visita. La ausencia puede interpretarse como falta de interés por la poca valía personal que entiende tener. Esto a su vez puede redundar en depresión. Si va a llegar tarde, aunque sea por 15 minutos, debe tomarse la molestia de llamar y comunicar la tardanza. Para evitar sentimientos de rechazo y disminución en la autoestima, el profesional debe informar al anciano(a) desde un principio, la duración del tratamiento. Otra cortesía básica es informar si va a tomar vacaciones o viajar al exterior.

- *Establecimiento y mantenimiento de la confianza:*

Es necesario desarrollar y mantener una relación de confianza mutua con el(la) anciano(a) antes de confrontarlo con la realidad del maltrato. Antes que nada, el profesional debe considerar la posibilidad de resolver la situación sin confrontaciones cuando entienda que el anciano(a) no podrá resistirlas. Si el anciano(a) es tratado en contra de su voluntad o no se cumplen las promesas hechas, puede experimentar ambivalencia y perder la capacidad de confiar en otros profesionales en el futuro. Esto puede llevarlo a aislarse aún mas, aumentando el riesgo del maltrato. Es importante recordar que una promesa incumplida es más perjudicial y dañina que el no hacer promesas.

- *Privacidad:*

El profesional debe intervenir con el(la) anciano(a) en un ambiente privado para promover la revelación de información que resulta dolorosa y sensitiva. Hay que recordar que los incidentes de maltrato por parte de una persona cercana, puede ser una experiencia sumamente vergonzosa y humillante para el(la) anciano(a). Según progresa el tratamiento y el(la) anciano(a) llega a confiar en la sinceridad del profesional de querer ayudar el victimario, pueden realizarse intervenciones conjuntas.

- *Aceptación:*

El profesional debe reconocer la necesidad que pueda tener el(la) anciano(a) de hablar y desahogarse, y sobre todo, su deseo de permanecer en control de su situación. Terminar con la relación abusiva puede tomar muchos meses. Durante ese tiempo, el(la) anciano(a) puede necesitar un visitante amigable y empático que escuche sus dudas, ansiedades, frustraciones y ambivalencias. El(la) anciano(a) puede aceptar la intervención más activa un poco más adelante, cuando sienta que ya está preparado y fortalecido.

La expresión y manejo de sentimiento puede llevar al anciano(a) a liberarse de sus tensiones, lo cual constituye una de las metas del tratamiento breve. El profesional debe validar los sentimientos y conflictos sin juzgar o reprochar, diciendo frases tales como, "A usted no le gusta que su hijo/a la amenace pero tampoco quiere separarse de el/ella o ir a un asilo." No debe confrontarse al anciano(a) cuando éste no está preparado para escucharlo. Debe permitírsele, además, proseguir la intervención cuando el anciano(a) esté receptivo a recibir la ayuda. Esto ayudará a desarrollar sentimientos de aceptación y le permitirá al anciano(a) mantener control de su tratamiento.

La meta inmediata después de un incidente de maltrato debe ser regresar al anciano(a) a un estado de equilibrio reduciendo la ansiedad y sentimientos depresivos. Se proponen tres factores para lograrlo: (1) ayudar al anciano(a) a obtener una percepción realista del suceso; (2) asegurarse que el anciano(a) tiene un sistema de apoyo adecuado, y (3) determinar si el anciano(a) posee mecanismos o destrezas de manejo eficacez.

Fuera del núcleo familiar, los recursos interpersonales e institucionales pueden ayudar al anciano(a) a desarrollar un patrón de búsqueda de ayuda. Grupos en la comunidad pueden proveer alivio, apoyo y satisfacción. Algunos(as) ancianos(as) se benefician de un cambio de residencia o convirtiendo su ambiente en uno más seguro cuando los amigos, vecinos y profesionales de diversas agencias llevan a cabo una intervención en conjunto.

Los(as) ancianos(as) se sienten más seguros cuando saben que su comunidad les proveerá la ayuda necesaria. El profesional, con la autorización del anciano(a), puede reclutar amigos y vecinos para que ofrezcan servicios esenciales. Los miembros de grupos cívicos o religiosos pueden transportar al anciano(a)

a diversas actividades, a citas médicas y tiendas, entre otros. Un grupo de apoyo comunitario puede contribuir significativamente a proteger al anciano(a), terminar el maltrato y mejorar la calidad de vida del anciano(a) y su familia.

EL CASO DE PUERTO RICO: LO QUE NOS MUESTRAN LAS ESTADISTICAS:

La situación del(la) anciano(a) puertorriqueño víctima de violencia, vía maltrato o abuso, se vislumbra como un problema sumamente serio. Datos de la Oficina para los Asuntos de la Vejez de P.R. presentan el siguiente panorama durante los años 1993 al 1997 (ver tablas suministradas):

1. Para los años de 1993 al 1997 el total de querellas de abuso hacia personas de edad - avanzada (60 años o más) fueron de 1,226 1,074, 1,768, 2,499 y 2,903 respectivamente. Hay que señalar que aún cuando existió una disminución en informes durante el año 1994 hay que ser suspicaces con dicha cifra, sobre todo al no tener un panorama muy extenso con qué comparar previamente (refiérase a Tabla I).

Tabla 1.
Total de querellas de abuso hacia personas de edad avanzada (60+) reportadas por agencias de área de envejecimiento
Oficina para los Asuntos de la Vejez - Oficina del Gobernador
Años Fiscales: 1993 a 1997

AÑO FISCAL	TOTAL DE QUERELLAS
1993	1,226
1994	1,074
1995	1,768
1966	2,499
1997	2,903

2. Aproximadamente el 95% del total de querellas de abuso son ocasionados por otras personas. El por ciento de autonegligencia está en aproximadamente un 5% (refiérase a Tabla II).

Tabla II.
Total de querellas de abuso a personas de edad avanzada (60+) por tipo de abusador reportadas por agencias de área de envejecimiento
Oficina para los Asuntos de la Vejez - Oficina del Gobernador
Año Fiscal: 1993 a 1997

AÑO FISCAL	TOTAL QUERELLAS	ABUSADO POR OTROS	AUTO NEGLIGENCIA
1993	1,226	1,172	54
1994	1,074	1,026	48
1995	1,768	1,675	93
1996	2,499	2,385	114
1997	2,903	2,796	107

Estos datos no incluyen información sobre querellas de abuso hacia personas de edad avanzada recopiladosa por el Programa Ombudsman de Cuidado de Larga Duración.

3. Las categorías más prevalentes de maltrato para todos los años informados son, en primer lugar negligencia y en segundo lugar abuso psicológico o emocional. (refiérase a Tabla III).

Tabla III.
Categorías de querellas de abuso hacia personas de edad avanzada (60+) reportadas por las agencias de área de envejecimiento
Oficina para los Asuntos de la Vejez - Oficina del Gobernador
Años Fiscales: 1993 a 1997

QUERELLAS REPORTADAS	AÑO FISCAL 1993	1994	1995	1996	1997
Abuso Físico	80	112	144	194	203
Negligencia (Pasiva/Activa)	753	470	810	1,013	1,169
Explotación material o financiera	110	149	180	310	365
Abuso psicológico \emocional	194	275	481	690	819
Abuso sexual	5	9	3	8	14
Otros tipos	84	59	150	284	333
Total	1,226	1,074	1,768	2,499	2,903

**Estos datos no incluyen la información de abuso a envejecientes en instituciones recopilada por el Programa Ombudsman de Cuidado de Larga Duración.*

4. Interesantemente, se encuentra que durante los años 1993 al 1995 y contrario a lo reportado en diferentes estudios en los Estados Unidos, Canada e Inglaterra donde el perpetrador más común es la esposa (o), en Puerto Rico los hijos son comúnmente los perpetradores. Sin embargo para los años del 1996 al 1997 se mantiene la tendencia de ser el cónyuge el perpetrador de abuso. (refiérase a Tabla IV).

Tabla IV.
Características del perpetrador de abuso hacia personas de edad avanzada (60+) repartidas por las agencias de área de envejecimiento
Oficina para los Asuntos de la Vejez - Oficina del Gobernador
Años Fiscales: 1993 a 1997

CARACTERISTICAS DEL PERPETRADOR	AÑO FISCAL 1993	1994	1995	1996	1997
Hijo/a	217	293	477	96	97
Esposo/a	16	45	103	683	817
Hermano/a	6	34	62	115	133
Nieto/a	14	41	59	68	71
Otro miembro familiar/conocido	45	57	122	140	175
Amigo/vecino	32	54	33	143	123
Proveedor de servicios voluntarios/privados	101	38	130	219	272
Otros	46	106	121	87	127
Total	477	668	1,107	1,553	1,782

**Estos datos no incluyen información sobre querellas de abuso hacia personas de edad avanzada recopilados por el Programa Ombudsman de Cuidado de Larga Duración.*

5. Las áreas con mayores querellas por maltrato para el período de 1993-1994 lo son: Humacao y Norte I. Para el período de 1995-96 lo son Bayamón y San Juan.

6. Los grupos de edad más afectados que solicitan una orden de protección durante los años 1994 a 1995 de 70-74 años, siguiéndole en orden los de 65-69 años y los de 60-64 años. Para 1996-1997 el grupo de edad fue el de 75-79 siguiéndole los de 70-74 y los de 80-84. (véase Tabla V y VI)

7. Las féminas son las que en su mayoría solicitan órdenes de protección (véase Tabla V).

El panorama presentado es un tanto desalentador sobre todo porque se reconoce que éstas no son las estadísticas reales del problema y sí sólo las informadas. Sin lugar a dudas deben existir más casos.

SUGERENCIAS Y CONCLUSIONES:

En Puerto Rico, al igual que en otros países, se requiere con carácter de urgencia, profundizar en el

Tabla V.
Total de envejecientes afectados por querellas de maltrato por grupos de edad reportados por las oficinas de Coordinación y Contacto con la Comunidad Envejeciente de las Agencias de Area de Envejecimiento
Oficina para los Asuntos de la vejez - Oficina del Gobernador
Año Fiscal 1996 - 1997

Grupos de Edad	Oficina de Coordinación y Contacto con la Comunidad Envejeciente (O.C.C.C.E.)																						
	Humacao		San Juan		Ponce		Guayama		Caguas		Mayaguez		Aguadilla		Carolina		Arecibo		Bayamón		Total		Total
	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F+M
60-64	2	4	30	23	21	7	4	1	10	3	16	8	15	6	7	6	5	3	50	26	160	87	247
65-69	4	1	23	16	8	6	9	4	17	11	16	5	8	4	25	9	4	1	46	17	160	74	234
70-74	2	1	44	17	4	8	2	5	18	9	11	9	13	5	28	17	5	3	63	29	190	103	293
75-79	1	1	41	28	9	12	12	3	12	7	36	11	7	6	19	7	4	2	48	28	189	105	294
80-84	2	2	43	17	15	4	3	8	14	9	18	13	14	7	2	13	4	5	57	35	172	113	285
85 +	2	2	35	20	9	5	6	8	17	8	15	11	6	9	11	10	4	4	46	22	151	99	250
Total	13	11	216	121	66	42	36	29	88	47	112	57	63	37	92	62	26	18	310	157	1022	581	1603
Total F + M	**24**		**337**		**108**		**65**		**135**		**169**		**100**		**154**		**44**		**467**		**1,603**		

Tabla VI.
Total de envejecientes afectados por querellas de protección por grupos de edad reportados por la Oficina de Coordinación y Contacto con la Comunidad Envejeciente de las Agencias de Area de Envejecimiento
Oficina para los Asuntos de la Vejez - Oficina del Gobernador
Año Fiscal 1994 - 1995

Grupos de Edad	Oficina de Coordinación y Contacto con la Comunidad Envejeciente (O.C.C.C.E.)																					
	Humacao		Metropol.		Ponce		Guayama		Caguas		Mayaguez		Aguadilla		Este		Norte II		Norte I		Total	
	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M
60-64	18	8	14	8	10	14	7	10	7	3	13	7	10	3	9	6	3	1	31	27	122	87
65-69	24	11	13	8	0	0	6	4	5	2	30	21	4	4	18	21	0	0	28	14	128	85
70-74	34	12	18	9	1	0	6	6	12	4	18	16	5	4	27	19	2	2	25	15	148	87
75-79	15	7	9	12	1	2	6	9	7	2	15	21	1	9	25	8	7	3	20	19	106	92
80-84	13	6	21	8	0	0	4	9	1	4	8	8	17	6	13	8	2	0	27	22	106	71
85 +	8	21	17	8	3	1	11	8	2	1	12	7	9	2	2	0	3	1	32	20	99	69
Total	112	65	92	53	15	17	40	46	34	16	96	80	46	28	94	62	17	7	163	117	709	491
Total F + M	**177**		**145**		**32**		**86**		**50**		**176**		**74**		**156**		**24**		**280**		**1,200**	

estudio de la violencia contra el(la) anciano(a) sobre todo haciendo énfasis en el maltrato y abuso contra éste. Conociendo más sobre el fenómeno, se puede dirigir esfuerzos a diseñar planes efectivos y eficientes de ayuda. De igual forma, es necesario crear programas efectivos para lidiar con este problema. Los programas institucionales que deben comenzar a crearse deben planificar y desarrollar proyectos que sean de carácter instrumental en la prevención y manejo del maltrato contra el(la) anciano(a). De igual forma dichos programas deben ser instrumento educativo para proveer orientación y concientización a los ciudadanos de edad avanzada. La educación es vital como elemento preventivo, campañas masivas de diferentes aspectos gerontológicos, y no solamente maltrato, deben ser desarrolladas. Se debe recibir adiestramientos de carácter intensivo donde se reconozca las múltiples facetas del problema y las alternativas más viables de acción. Es importante reconocer que el fortalecer los lazos familiares es vital para disminuir el maltrato en los(as) ancianos.

Se debe aceptar el utilizar aquellas instituciones, agencias o programas que provean alternativas para poder manejar de forma menos estresante, aquellos problemas que se puedan tener en las familias. Esto puede hacer la diferencia al momento de lidiar efectivamente con el problema. Hay que recordar que de los factores altamente correlacionados con el maltrato, uno de los más importantes es la necesidad de los(as) ancianos(as) y su familia de redes de apoyo que los ayuden a cubrir apropiadamente sus necesidades.

Recordar que mientras más autosuficientes sean los(as) ancianos(as), menos probabilidad de que sean maltratados en cualquier lugar. Se debe ejercer presión para que se creen, fortalezcan y hagan cumplir las leyes contra el maltrato doméstico. Si se conoce de algún caso meritorio, se debe buscar orientación y ayuda en términos de los pasos a seguir.

Recordar que para disminuir el maltrato es fundamental que se empiece a combatir el aislamiento en que el(la) anciano(a) va sumiéndose según va aumentando su edad. De igual forma, es necesario proveerle a los(as) ancianos(as) la oportunidad de una vida más digna a través del respeto de sus derechos. Cuando se comience a modificar la percepción de que el anciano(a) será a la larga un estorbo social y se provea aquella ayuda necesaria para mejorar su calidad de vida, en ese momento se comenzará a ver una disminución del maltrato contra el(la) anciano(a). Los gobiernos requieren comenzar a diseñar programas de ayuda a largo plazo que realmente funcionen para no sólo prevenir, sino intervenir con el problema. A la sociedad le corresponde dicha tarea; esa debe ser la meta.

REFERENCIAS

1. Vázquez-Calzada, J.L. La población de Puerto Rico y su trayectoria histórica. Escuela Graduada de Salud Pública. 1era Edición Universidad de Puerto Rico. 1989: 1 Río Piedras, Puerto Rico.
2. Alsina Pomales, S. y Rodríguez-Gómez, J.R. El suicidio en Ancianos Puertorriqueños, Revista Latinoamericana de Psicología. 1995: 27, 263-282.
3. Oficina para Asuntos de la Vejez. Perfil demográfico de la población Envejeciente 1990. División de Planificación, Investigacaciones y Estadísticas, Oficina del Gobernador. San Juan, P.R. 1994: 1
4. Stark, E. y Flitcraft, A. Violence among initmates; An epidemiological review. En Van Hasselt V.B., Morrison, M. (Eds). Handbook of Familyviolence. New York Plenum Press. 1988: 293 317
5. Ramos, H. Indicadores de maltrato en una población de hombres y mujeres viejos en los centros de cuidado en Ponce. 1991 Disertación sin Publicar. Centro Caribeño de Estudios Postgraduados. San Juan, P.R.
6. Penhale, B. The Abuse of Elderly People: Considerations for Practice. British Journal of Social Work. 1993: 23, 95-112.
7. O'Malley, H.C., Segel, H.D. y Pérez, R. Elder Abuse in Massachusetts: A survery of professionals and paraprofessionals. Boston: Legal Research and Service for the Elderly. 1997:20
8. Steuer, J. y Austin, E. Family abuse ofthe elderly. J. Ame. Ger. Soc. 1980:28, 372-276.
9. Gioglio, G. y Blakemore, P.R. Elder Abuse in New Jersey: The knowledge and Experience of Abuse among Older New Jerseyans. Trento, N.J.: Department of Health Services. 1983: 12
10. Callaham, R. y Blakely, B. Elder Abuse and Neglect: A Study of Adult Protective Service Workers in the United States. J. of Elders Abuse & Neglect. 1989: 1, 3: 31-49.
11. Freeman, M. Violence in the Home. Saxon House. England. 1979: 16
12. Gelles, R. Family Violence. Second Edition. Sage Library of Social Rearch, Newbury Park. 1991: 1
13. Nazario, J. y Rodríguez-Gómez, J.R. Reconceptualización Cognitiva en la percepción de la actividad sexual de los ancianos: neoformación estructural de actitudes hacia la sexualidad en la vejez. Boletín Asociación Médica de Puerto Rico. 1996: 88 No. 10-11-12: 94 -98.
14. Holt, M.G. Elder Sexual Abuse in Britain: Preliminary Findings, J. of Elders Abuse & Neglect. 1983; 5, 63-71
15. Pritchard, J.The Abuse of Older People (2nd edition). Jessica Kingsley Publishers. London, England. 1995:75
16. Ammerman, R.T. y Hersen, M. Treatment of Familiy Violence: A Sourcebok. New York, John Wiley. 1990: 18
17. Pillemer, K. y Finkelhor, D The Prevalence of Elder a Buse: A random Sample Survey. Gerontologist. 1988: 28, 51-57.
18. Ogg., J. y Bennett, G. Elder Abuse in Britain. Brit. Med. Journal. 1992: 305, 988-989.
19. Podkieks, E. National Survey on Abuse of the Elderly in Canada. J. of Elders Abuse and Neglect. 1992: 4, 55-58.
20. Rodríguez, J. El Abuso del Anciano en Puerto Rico. (1997). Documento inédito. San Juan, Puerto Rico.

Vol. 90 • 7-8-9-10-11-12 / 1998 • Pág. 154, 157

Artículos Especiales:

El Mito sobre la Remoción Involuntaria de Organos para Trasplante

Eduardo A. Santiago Delpín, MD, MS[1]

Periódicamente, y a pesar de que ha sido continuamente aclarado durante los últimos diez años, resurge un mito que se niega a desaparecer sobre la remoción involuntaria de órganos para transplante. Este mito toma dos vertientes, a saber, niños que secuestran para removerle los órganos "para enviarlos a los países capitalistas, usualmente los Estados Unidos", y el individuo que se va con una dama desconocida a tomar un trago y despierta en la tina del baño de un hotel, cubierto de hielo, con un teléfono al lado y una nota que lee "a usted se le removió un riñón, llame al número 911 para que le atiendan". Desafortunadamente, las historias se repiten incluso en revistas y periódicos de reputación, y más recientemente en el Internet. El Internet tiene el peligro adicional de que cualquier persona con cualquier idea, por más aberrante y pervertida que sea, puede convertirse en su propio editor y publicador.

Todas las historias, acusaciones, alegaciones y rumores relacionados con América Latina han sido investigadas en los últimos once años y encontradas falsas. En algunas, la fuente del rumor nunca se encontró ("un amigo de otro amigo de mi prima que le dijo que había escuchado..."); o la fuente original se retractó (los casos de Honduras y Costa Rica); o se determinó engaño por parte del perjudicado (la supuesta remoción de córneas en Argentina y en Chile). Todas son falsas, y sin embargo la mayoría de la gente las cree y las repite, incluyendo a profesionales.

Existe comercio de riñones voluntario y pago en la India, y comercio involuntario de órganos de prisioneros ejecutados en China. En India, donde hasta hace muy poco no existía una ley que permitiera la donación cadavérica, un donante voluntariamente vende su órgano para transplantarse a una persona pudiente. Esta práctica resulta en complicaciones infecciosas y viola principios bioéticos de importancia, y ha sido condenado por la mayor parte de las organizaciones mundiales. En China, se le extraen los órganos a prisioneros ejecutados. Además de violar ciertos derechos, esta práctica también viola principios bioéticos y ha sido condenada también por países y por organizaciones internacionales.

Pero esto es en India y China, y no es a esto que se refieren los rumores que aparecen en el Internet y en la prensa sensacionalista.

A continuación enumeramos algunos datos de importancia para poder evaluar con seriedad y conocimiento estos rumores, ya que el repetir rumores de esta naturaleza demuestra superficialidad y falta de visión crítica, además de que crea un clima de desconfianza que hace daño a los pacientes que están en listas de espera para recibir transplante de órganos.

I. En relación a la cirugía del donante y el recipiente

A. El remover un riñón que funcione al transplantarse, sin hacer daño a un donante vivo requiere una sala de operaciones equipada: mesa quirúrgica, equipo y monitores de anestesia, cauterio, instrumental quirúrgico y materiales. Requiere también un equipo de resucitación.

B. Extraer un órgano que funcione luego del transplante requiere cirujanos altamente adiestrados en la técnica de remover estos órganos sin causarles daño, o sea, conocimientos y destrezas adicionales que no se encuentran en el cirujano o técnico usual. Transplantar un órgano - bien sea corazón, pulmón, hígado o riñón es una especialidad quirúrgica reconocida que requiere años de entrenamiento en programas específicamente aprobados para aprender esta especialidad.

C. Que el donante sobreviva la operación requiere además personal altamente adiestrado en anestesiología y en el manejo específico del donante.

D. Miremos la logística necesaria para cumplir con los estos requisitos:

1. Extraer un órgano en el mismo plantel que se trasplanta requeriría una movilización extraordinaria de donantes, recipientes y facilidades hospitalarias. En el caso del corazón, pulmón e hígado se requiere además facilidades de

[1] *Programa de Trasplante de Puerto Rico, Hospital Auxilio Mutuo y Departamento de Cirugía. Universidad de Puerto Rico, San Juan, Puerto Rico.*

cuidado intensivo con intensivistas y especialistas en el órgano concernido. Estas son operaciones que no pueden realizarse en una casa, en una habitación de un hotel o en una clínica clandestina en la frontera con algún país.

2. Extraer el órgano en un plantel para enviarlo a un hospital requeriría el equipo de sala de operaciones arriba descrito y unas facilidades imposibles de ocultar en una habitación de un hotel...a menos que los hoteles sean partícipes de este gran complot...

3. Si el órgano se extrae en otro lugar distante al hotel, traer luego a un donante dormido, en una camilla, y pasearlo por el vestíbulo, subirlo en un elevador a la habitación del hotel, preparar la tina donde se va a depositar este cuerpo recién salido de anestesia, sería una secuencia altamente bizarra, inusual y sospechosa para los oficiales del hotel. De nuevo habría que invocar un extraordinario complot con los hoteles.

4. Inmersión en agua helada a una persona dormida resulta en rápida disminución de la temperatura corporal y pronta muerte. Estas muertes no han sido informadas ni por las fiscalías ni por los forenses de ningún estado o país del mundo. De haber ocurrido muertes que se oculten, implicaría a médicos, forenses y a la policía concernida como cómplices de un magno complot.

5. Aunque el tiempo que tolera un riñón fuera del cuerpo es variable, es muy limitado para el corazón, pulmón, páncreas, intestino e hígado. Esto significa que la operación del donante y del recipiente tienen que realizarse en lugares lo más cercanos posible, o si no contar con servicios de jets privados continuamente. ¿Están involucrados en el complot también?

6. Los líquidos y las máquinas de preservar órganos provienen de compañías reglamentadas por la industria y el gobierno. Usualmente los clientes son miembros conocidos por la comunidad de transplantes. ¿Participan también las compañías de preservación de este complot?

II. Relacionado al supuesto "mercado" para estos órganos:

A. Cada vez que una persona recibe un transplante, o se retira de una lista de espera, o sale de un cuidado intensivo, o sale de diálisis. Las listas de espera y los registros de transplantes son estrictamente controlados por las sociedades profesionales o por los gobiernos. Igualmente, los médicos de los intensivos y los nefrólogos de los pacientes que reciben diálisis sospecharían al ver a su paciente desaparecer súbitamente, y luego aparecer vivo y saludable. El control de los intensivos y de los registros es rígido y estricto. Implicaría que los gobiernos, y los hospitales estarían también en este complot, conjuntamente con las fiscalías, los hoteles y la policía que mencionamos anteriormente.

B. Los corazones, hígados y pulmones de niños sirven solamente para niños y ocasionalmente para adultos muy pequeños. Los riñones pareados pueden ser trasplantados a adultos pequeños. Es difícil concebir un mercado de niños para transplante de órganos cuando en realidad su uso está limitado tan sólo a riñones.

C. La industria de los inmunosupresores usualmente lleva un registro del movimiento de sus medicamentos bien sea a instituciones, farmacias o gobiernos. Estos a su vez lo dispensan a pacientes a través de recetas controladas. ¿Está también envuelta la industria farmacéutica en este gran complot?

Suena ridículo y sin embargo lo creemos y lo que es peor, lo repetimos, incluso prensa responsable, escritores inteligentes y hasta profesionales de la salud. Esto refleja falta de discriminación y de evaluación crítica de lo que se está repitiendo. Probablemente las malas noticias de la prensa, la visión negativa que tenemos de nosotros mismos continuamente por los medios noticiosos, las novelas y películas que describen tantos horrores, nos han desensibilizado de tal manera que nos es sencillo creer automáticamente que puedan ocurrir aberraciones como las arriba descritas. Cuando se somete la noticia a un escrutinio crítico como el arriba descrito nos sorprendemos que hayamos podido creer esta fabricación y nos vienen a la mente preguntas tales como, ¿qué mente aberrante puede haberlas fabricado? ¿Cuál es el motivo de esta publicidad? Es obvio y hay evidencia de que en algunos lugares ha habido una ganancia secundaria importante económica o política, pero esta ganancia ha sido a expensas de un daño que no tiene remedio.

El daño principal de la repetición indiscriminada de rumores falsos ha sido a los pacientes que están en lista de espera para transplante de órganos, y que dependen de donación altruista y voluntaria. Al popularizarse el mito en un país dado, ocurre una disminución en las donaciones y ocurren muertes de pacientes en listas de espera. Así, indirectamente, estos rumores están causando muerte a personas que necesitan un órgano. En este sentido los rumores pueden ser considerados como criminales.

Peor aún, los rumores atentan contra el mensaje humanista y hermoso que transmiten a la humanidad los transplantes y las donaciones: el pensamiento de que todavía existe la bondad, el altruismo y el

heroísmo de personas que se someten a cirugía para aliviar la salud de un ser amado, y de otras personas que vencen el sufrimiento del luto para dar vida a un desconocido.

Parafraseando al Papa Juan Pablo II ante la Organización Internacional de Obtención de Organos en el 1992, "la donación de órganos es lo más que se acerca al espíritu cristiano porque si Cristo dio su vida por la humanidad, es cristiano que un ser humano dé un órgano o el órgano de un ser querido para que viva su semejante". Es contra este mensaje y contra la bondad y los más altos valores espirituales que atenta este mito.

Como profesionales de la salud no podemos permitir que se perpetúe un rumor que es falso, que hace daño, que atenta contra la vida de las personas en la lista de espera, y que transgrede las aspiraciones más nobles de la humanidad.

Bibliografía:

1. AP (Guatemala City): American Woman in Serious Condition After Being Beaten by Guatemalans, *The San Juan Star,* March 31, 1994, p 16.

2. Basler B: Kidney Transplants in China Raise Concern About Source, *The New York Times,* June 3, 1991.

3. British Transplantation Society: BMJ 293:257, 1986.

4. Brookes S: The Body Brokers: Grisly Trade in Human Organs, Insight, June 8, 1992, p 7.

5. Cerilli J: Transplantation 46:171, 1988.

6. Colindres F, Morales C: ¿Tráfico de Organos en Guatemala? *El Nuevo Herald,* June 23, 1994, p 9A.

7. Connell ML: Why not a market for human organs? *The Miami Herald,* March 29, 1992, C-l.

8. Daar AS, Sells RA: Transplant Rev 4:128, 1990.

9. Dickerson AJ: (AP) Detroit, Una Posibilidad Cuestionable el Comercio de Organos, *El Nuevo Día* (Puerto Rico), Sept 24, 1991, p 34.

10. Dickerson B: Should Organs be Taken from Executed Killers?, *The Miami Herald,* Oct 15, 1985, p 17A.

11. Documentary on Organ Trade Provokes World-Wide Outrage Calls for Action. Transplant News 3(22): 5, 1993.

12. Dossetor JB, Manickavel V: Transplant Proc 23:2508, 1991.

13. Eurosciences Media Workshop: Report by Mr. Eric Sottas, Director, World Organization Against Torture, 7 March 1994.

14. Fuenzalida-Puelma HL: Bull Ofic Sanit Pan Am 108:445, 1990.

15. García C: Biológicamente no es Posible el Comercio de Organos, *El -Día* (México), Aug 6, 1992, p 3.

16. Gedda G: (AP, Washington), Rumors of U.S. Baby Snatchers Incite Guatemalans to Violence, *The San Juan Star,* March 30, 1994, p 20.

17. Guttman RD: Transplant Rev 6:189, 1992.

18. Hedges C: Egypt's Doctors Impose Kidney Transplant Curbs, *New York Times,* Jan 22, 1992.

19. Hirandani LH: The Kidney Traders, *Indian Express,* July 18, 1989.

20. Hsieh H, Yu TH, Yang WC, et al: Transplant Proc 24:1335, 1992.

21. Jackson I (Editor): The Body Parts Business. (Video), Alma Productions, Ontario Ltd. 1994.

22. Juarez CJM: Imposible Científicamente Traficar Organos Humanos, *Novedad* (México), Sept 6, 1983, p 15.

23. Leventhal T: The "Baby Parts" Myth: The Anatomy of A Rumor, UNOS UPDATE, May 1994, pp 2-5.

24. María M: (EFE), El Tráfico de Organos Humanos en el Tercer Mundo, La Semana (Caguas, Puerto Rico), July 4, 1991, p 22.

25. Martínez I: ¡Devuélvanme mi Riñón...! *El Nacional* (Caracas, Venezuela), March 13, 1991, p C-1.

26. Martínez S: Niños de Repuesto: Proceso 918, June 6, 1994.

27. Needed: A Campaign for Cadaver Donations, *The Hindu,* Aug. 19, 1990 p 18.

28. OEM, Niega el Director del Registro de Tratamiento Tráfico de Organos en el Territorio Nacional, *El Sol de México,* June 14, 1994, p 4.

29. Pan American Transplant Organization Publishes Ethics Document, UNOS Bull, Feb/Mar 1989.

30. Perera V: Behind the Kidnapping of Children for Their Organs, L.A. *Times,* May 1, 1994, p M-1.

31. Peters TG: JAMA 265:1302, 1991.

32. Santiago Delpín EA: Donación Cadavérica: ¿Debemos permitir la Comercialización? *Prensa Médica* (Asociación Médica de Puerto Rico), 1991, p 11.

33. Santiago Delpín, EA, Allegations of Organ Commerce in Middle America, Transplant Proc 1996, 28:3370-3373.

34. Santiago Delpín, EA, Editorial: Regarding the Bellagio Task Force on Organ Commerce, Transplant Proc, in press.

35. Santiago Delpín, EA, Guideline to Assist Authorities in Each country with regards to transplantation, Transplant Bull. 1997, 6:9-11.

36. Santiago Delpín, EA, La Donación de Vivo Relacionado Emocionalmente: Virtudes y Peligros, Nefrología Latinoamericana, en Imprenta, 1988.

37. Santiago-Delpín EA: Organ Donation in Latin America Transplant Proc 23:2516, 1991.

38. Schneider A, Flaherty MP: Donating Your Kidney for Funds and Profit - The Rapacious Trade in Organs, *The San Juan Star,* Nov 3, 1985, p 18.

39. Schneider A, Flaherty MP: Haitians Sell Their Own Kidneys for Transplants in U.S., *The San Juan Star,* April 6, 1985, P.5.

40. Should Families be Offered Money for Cadaver Organs? AMA *News,* March 18, 1991, p 37.

41. Silva V: (UPI, Lima, Perú), Archbishop Says Latin American Children Killed for Organs, UPI International Newswire, May 2,1991.

42. Soviet Influence Activities: A Report on Active Measures and Propaganda, 1987-1988, US Department of State Publication #9720, Bureau of Intelligence and Research, Aug 1989.

43. The Council of the Transplantation Society: Lancet Sept 28, 1985, p 715.

44. United Nations, Economic And Social Council: Commission on Human Rights, Forty-Seventh Session, Agenda Item #12, Sale of Children, Report Sumbmitted by Mr. Vitit Muntabhorn, UN/E/CN. 4/1991/51, Jan 28, 1991.

45. Valero C:(EFE, Geneva), América Latina: Meca del Tráfico de Organos, *El Nuevo Día* (Puerto Rico), Aug 4, 1991, p 48.

46. Valles DA: Se Confirma el Tráfico de Niños en México, *El Nuevo Día* (Puerto Rico), April 17, 1993, p 28.

47. World Health Organization, Eighty Seventh Session, Human Organ Transplantation, Resolutions WHA 40,13 (Guiding Principles) and WHA 42.5 (Organ Commerce), Nov 19, 1990.

48. World Health Organization, Second Informal Consultation on Organ Transplantation. WHO/HLE/90.2/Annex 4. Resolution WHA 42.5 (Preventing the Purchase and Sale of Human Organs), Oct 3, 1990.

49. World Health Organization: Human Organ Transplantation, A Report on Developments Under the Auspices of W.H.O. (1987 1991), WHO-Geneva.

Artículos Especiales:

The Relationship Between the Profile of Severity of Addiction and the Retention of Patients in the Ambulatory Program of DDTP

Done by: Erick F. Santos, M.D.,M.P.H.
María de L. Martínez, M.D.; Linés M. Pérez, M.D.

Summary

Objectives: *the authors described some variables related to the retention of drug dependent veterans receiving outpatient treatment at San Juan V.A.M.C. and compared the profile of addiction severity with retention using a global dysfunction scale.*

Methods: *the clinical charts of 74 patients were examined at random using a 16-item questionnaire based on the ASI scale. The data was processed and analyzed using the Epi Info V6.2 computer program, utilizing chi square as the main statistics.*

Results: *the patient's retention in treatment for > or = to 3 months was associated with some specific variables such as: more than 12 years of education, being catholic, divorced, living with parents, use of more than one drug of preference, having a negative urine toxicology result before treatment and after treatment, and showing a favorable change in urine toxicology results. In terms of severity of dysfunction, a considerable substance problem and an extreme legal problem were associated with a retention of > or = to 3 months, as well as no evidence of occupational problems.*

Conclusion: *The strong correlation between specific variables and the retention of patients in treatment for > or = to 3 months should create awareness of the importance of available and effective treatments in the fight against substance abuse and mental health problems as well as to educate and integrate family members in patients treatment, since a supportive family member is one of the best tools that patients and therapist can have to help maintain patient's sobriety.*

INTRODUCTION:

As clinicians of the psychiatric field, concerned about addictive disorders, the investigators have noticed that patients who stay on treatment tend to show improvement in their psychosocial functioning. Evidently, those patients who remain on treatment see their participation useful and necessary for their recovery. We can say, safely, that their behavior of retention in treatment can be enhanced by strengthening of some personal factors in patients and their environment, some characteristics of therapists and some of the therapeutic environment. The authors main area of concern in this study are the demographic characteristics of patients and their association with their retention in treatment (1).

The investigators consider this study as a basic one in the understanding of this population and in finding adequate ways of health promotion and treatment of their addictive disorders. The modern literature considers the issue of retention in treatment as crucial for good outcomes of patients with drug addiction, as well as necessary to understand how to improve strategical interventions for those patients who dropout from treatment. Then, the study is clearly significant and pertinent to the current interests of all health professionals, particularly those involved in the care of patients with substance use disorders (2) (3) (4) (5).

The authors delineated the following investigation hypotheses:

1. The demographic characteristics of patients -on admission-, are associated with their retention in treatment.
2. The severity profile of patients -on admission-, is associated with their retention in treatment.

The specific objectives of the study were:

1. To describe some demographic variables of veterans with drug addiction in the outpatient treatment clinic of the San Juan V.A.M.C. during fiscal year of 1996.
2. To determine the association between the severity profile of addicted veterans with their retention in treatment at the San Juan V.A.M.C. outpatient drug dependence treatment clinic during the fiscal year of 1996.
3. To determine the association between the demographic variables of addicted veterans of the outpatient treatment clinic of the San Juan V.A.M.C. with their retention in treatment during the fiscal year of 1996.

METHODOLOGY:

This is a retrospective, descriptive and observational study about the demographic profile of drug dependent veterans, the association between their demography and their retention in an outpatient

Mainly, the sample was married, followed by divorced (Table I), although 18.9% were single and 17.6% separated. The majority of our sample lived with a partner or with parents (Table I) and 17.6% lived with other family member, also 10.8% lived alone and 8.1% lived in a controlled environment.

The chief complaint of the patient and the diagnosis of the psychiatrist determined the drug of preference. More than half of patients preferred the use of more than one drug (Table I). The majority of the patients had positive urine toxicology results before treatment (Table I). After treatment, the amount of negative urine toxicology results increased, suggesting that, in general, the treatment had a good effect on reducing substance use of patients.

We considered a retention of 3 months or more as the cut off point from which outcome could be predicted (Table I). In the literature was described that retention of 3 months or more is associated with better outcome.

Table I
Demographic profile of patients treated in DDTP from October 1996 to September 1997
(Data taken from admission notes)

Mean age	39.9 years old
Percent of patients with ≤ 12 years of school	48.6%
Percent of patients with > 12 years of school	51.4%
Unemployed	60.8%
Retired	21.6%
Catholic	51.4%
Protestant	24.3%
Married	40.5%
Divorced	21.6%
Living with partner	36.5%
Living with parents	25.7%
Prefer the use of > 1 drug	58.1%
Prefer the use of cocaine	14.9%
Prefer the use of heroine	13.5%
Positive urine toxicology at admission	62.2%
Negative urine toxicology at admission	37.8%
Positive urine toxicology at the end of treatment	48.6%
Negative urine toxicology at the end of treatment	47.3%
Remained < 3 months	45.9%
Remained ≥ 3 months	54.1%

We separated the sample into this two groups of retention (> or = to 3 months and < of 3 months) to compare demographic profile and severity of dysfunction. In terms of the relationship between age and retention, we found that the sample was homogeneous with a mean age of 39.97 for patients that stayed < 3 months and 38.85 for patients that stayed > or = to 3 months. We found a significance in the association of educational level and retention. The sample that stayed > or = to 3 months showed a tendency to have more than 12 years of education (Table II).

Table II
Relationship between Education Level and Retention

	Elemental	Secondary	High School	University
< 3 months	n (%) 1 (2.9)	n (%) 3 (8.8)	n (%) 15 (44.1)	n (%) 15 (44.1)
>= 3 months	1 (2.7)	0 (0)	13 (35.1)	23 (62.2)

x2 = 4.709
p = .194

For the group of retention of > or = to 3 months, most lived either with parents or with partner (Table III). For the group that stayed < 3 months, they lived mainly with a partner or with a relative. We found a clinical significance among patients living with parents, showing a tendency of these patients to remain more in treatment.

Table III
Relationship between living arrangement and Retention

	Alone	Partner	Family	Friends	Parents	Cont. Env.
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
<3 months	3(8.8)	14(41.2)	7(20.6)	1(2.9)	6(17.6)	3(8.8)
≥3 months	5(12.5)	13(32.5)	6(15.0)	0(0)	13(32.5)	3(7.5)

X2 = 3.73
p = 0.5887

For the group that stayed > or = to 3 months, 37.5% were married, 27.5% divorced, 17.5% single, 15.0% separated and 2.5% widow. For the subjects that stayed < 3 months, 44.1% were married, 20.6% were either single or separated, and 14.7% were divorced. We found a significance in the tendency of divorced patients to remain in treatment. In terms of type of work, in the group that remained > or = to 3 months 65.0% were unemployed and 22.5% were retired. For the group that remained < 3 months 57.6% were unemployed and 21.2% were retired, showing that the population was homogeneous for both groups of retention.

In terms of religion we found for the group that stayed > or = to 3 months that 60.5% were catholic, 26.1% Protestant and 13.2% did not practice any religion. For the patients that stayed < 3 months 48.4% were catholic, 29.0% Protestant and 19.4% not practice any religion. We found that patients that remained > or = to 3 months had a tendency to practice catholic religion, showing a clinical significance between both groups.

We found a significance on the tendency for the group that stayed > or = to 3 months to prefer the use

of more than one drug, and a tendency for the group that stayed < 3 months to prefer the use of heroine (Table IV).

Table IV
Relationship between Drug of Preference and Retention

	Alcohol	Heroin	Cocaine	Marihuana	Sedates	Others
< 3	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
months	1 (2.9)	7 (20.6)	6 (17.6)	0 (0)	3 (8.8)	17(50.0)
>= 3 months	3 (7.5)	3 (7.5)	5 (12.5)	2 (5.0)	1 (2.5)	26 (65.0)

X2 = 7.14
p = 0.2108

It was significant the correlation between a negative result before treatment and retention > or = to 3 months as well as a positive result before treatment and retention < 3 months (Table V). For urine toxicology after treatment (Table VI), it was very significant (p=>.000) the tendency of patients that stayed > or = to 3 months to have negative results, and the tendency of patients that stayed < 3 months to have positive results. These findings were consistent with the correlation of outcome with a retention of > or = to 3 months. Consistent with the above results and with clinical and statistical (p=.001) significance, it was found a tendency of patients that stayed > or = to 3 months to have a favorable change in the urine toxicology throughout the treatment, and also the tendency of patients that stayed < 3 months to have a urine toxicology change that indicated a worsening in patient's condition (Table VII).

As previously discussed, another of our objectives was to correlate the severity of dysfunction in these patients with retention. We found homogeneous results of the severity of medical problems in both groups of retention. The severity of these problems is variable. About psychiatric problems and retention, it had also homogeneous results; however, the majority of the patients were affected from a moderate to an extreme extent by psychiatric problems. Extreme substance abuse problems were related to retention < 3 months, but considerable problems were significantly associated with retention > or = to 3 months (Table VIII). The severity of legal problems, when correlated to retention, showed a marked significant tendency of patients with considerable legal problems to stay in treatment < 3 months, and of patients with extreme legal problems to stay > or = to 3 months (p=.009, see Table IX). The severity of family problems was variable among these patients. Finally, it was significant that having no occupational problems helped patients to stay > or = to 3 months, but considerable occupational problems resulted in short retention of patients, (Table X).

Table V
Relationship between Toxicology Before Treatment and Retention

	Negative	Positive
< 3	n (%)	n (%)
months	11 (32.4)	23 (67.6)
>= 3 months	17 (42.5)	23 (57.5)

X2 = 0.80
p = 0.370

Table VI
Relationship between Toxicology After Treatment and Retention

	Negative	Positive
< 3	n (%)	n (%)
months	8 (25.8)	23 (74.2)
>= 3 months	27 (67.5)	13 (32.5)

X2 = 12.15
p = 0.00049

Table VII
Relationship between Toxicology change and Retention

	Negative Change	Positive Change
< 3	n (%)	n (%)
months	23 (74.2)	8 (25.8)
>= 3 months	13 (32.5)	27 (67.5)

Legend:
+Change = ToxBefore-/ToxAfter- ToxBefore+/ToxAfter-
-Change = ToxBefore+/ToxAfter+ ToxBefore-/ToxAfter+

X2 = 12.15
p = 0.00049

Table VIII
Relationship between Substance Problems and Retention

	None	Mild	Moderate	Considerable	Extreme
< 3	n (%)	n (%)	n (%)	n (%)	n (%)
months	0 (0)	1 (2.9)	5 (14.7)	9 (26.5)	19 (55.9)
>= 3 months	1(2.5)	1 (2.5)	9 (22.5)	15 (37.5)	14 (35.0)

X2 = 3.94
p = 0.4142

Table IX Relationship between Legal Problems and Retention					
	None	Mild	Moderate	Considerable	Extreme
< 3 months	n (%) 24 (70.6)	n (%) 3 (8.8)	n (%) 3 (8.8)	n (%) 4 (11.8)	n (%) 0 (0)
>= 3 months	29 (72.5)	5 (12.5)	0 (0)	0 (0)	6 (15.0)
X2 = 13.57 p = 0.00878					

Table X Relationship between Occupational Problems and Retention					
	None	Mild	Moderate	Considerable	Extreme
< 3 months	n (%) 7 (21.2)	n (%) 3 (9.1)	n (%) 6 (18.2)	n (%) 12 (36.4)	n (%) 5 (15.2)
>= 3 months	16 (40.0)	6 (15.0)	4 (10.0)	10 (25.0)	4 (10.0)
X2 = 4.59 p = 0.3325					

DISCUSSION:

There were variables that resulted to be homogeneous among the two groups of retention, these were age, type of work, that describe common characteristics of the population of this clinic. Also medical problems resulted to be homogeneous in the sample, but showed that these patients have a variety of medical conditions that have to be evaluated and treated. This is also true for the psychiatry problems that were not related to retention time but showed that the majority of the patients have significant psychiatry symptoms, including the cases of dual diagnosis (6). Family problems were found to be homogeneous among the groups of retention but also show a variety of the degree of severity, so is important to satisfy the needs of family support and education. Other variables showed clinical significance, giving us predictive and preventive hints to intervene effectively with patients with substance dependence problems. More than 12 years of education was related to longer retention time. This is consistent with the association between no occupational problems and more retention. Patients with less than 12 years of education and/or occupational problems require more attention in these areas to continue in treatment, so that they would have a better outcome. The service of counselors, vocational rehabilitation and social worker are thus considered necessary.

It was interesting the association of being catholic and more retention time, opening a research avenue for new questions about what type of religious practices influence the retention and outcome of patients in this type of clinic. A divorced status was associated with more retention. This is an unusual finding. We expected married patients to have more retention, but in this classification we only counted those patients that were legally married in which no increase in retention was found. Consensual relationship was counted when we joined the legally married and those living consensual as the variable living with partner. This was associated with better retention. For the majority of these patients that were unemployed, divorced, separated, or had another psychiatry condition their parents was the primary support group that helped them to continue in treatment.

Although it was surprising to find that patients with more retention preferred the use of more than one drug, we postulate that the effect of one drug may interfere with the effects of the other drugs, it may also produce relief of withdrawal symptoms and craving, for example: cocaine have clonidine-like effects that can relief heroine withdrawal symptoms and alcohol craving. On the other hand, the use of heroine associated with less retention can be explained by the severity of withdrawal symptoms that impedes patients to stop using the drug. It is thus valuable to do detoxification from substances before outpatients treatment begins, because negative urine toxicology results can predispose the patients to have a better outcome (7).

Considering urine toxicology as one measurement of outcome, our findings agree with the fact that more retention is associated with better outcomes. The positive change in urine toxicology underlines the importance of stimulating abstinence in this patients as soon as possible after their initiation of outpatient treatment.

Our hypotheses were proved in terms of the relationship between the degree of substance use problems and retention. Having extreme problems influence the patient to drop out from treatment because they usually have a lot of somatic distress, poor impulse control and probably needed to be referred to a controlled environment or hospitalization or even other type of clinic as methadone maintenance treatment. Frequently, these severely affected patients refuse our advice to enter a more controlled treatment setting.

We found legal problems to stimulate retention of patients, because in an extreme situation they are forced to receive treatment. If the legal problems are considerable they have no obligation to assist to the clinic. We can speculate that if the patients are forced to receive treatment before their legal problems

become so severe, they will probably improve from their substance dependence condition.

CONCLUSION:

The strong association between specific variables and the retention of patients in treatment for > or = to 3 months should create awareness of the importance of availability of effective treatments in the fight against substance abuse and mental health problems. A supportive family member is one of the best tools that patients and therapist can have to help maintain patients sobriety and his/her participation is essential for better outcomes (8)(9).

Also, every professional should stimulate these patients to improve occupationally and academically.

Our study suggest that we should continue reinforcing the special courts that treat cases related to the substance use, to promote the retention of patients in treatment and thereby improve their outcome. Also we should continue giving support to the programs of vocational rehabilitation to improve the educational and productive capacity of the patients.

The study supports the development of other alternatives in treatment that can respond to the special necessities of the addicted population for long-term treatment. Also, it is very important to reinforce the education of the partners, family and other significant persons in the life of the patient, so that the patients could be retained more time in treatment.

Some recommendations about future studies should be to increase the amount of charts in the sample, use the Addiction Severity Index Scale, and include and design other types of scales to further clarify in what way the variables influence outcomes in this population.

Acknoledgment: *We give special thanks to Víctor Tirado, M.D., for his dedication in helping in the recollection of data in this study. Also, we'd like to thank Michael Vélez for helping us in the statistical analysis process.*

Resumen
Objetivos: *Los autores describen algunas de las variables asociadas a la retención de pacientes veteranos con adicción a drogas en tratamiento ambulatorio en la clínica DDTP del Hospital de Veteranos. También comparan el perfil de severidad de adicción entre dos grupos de retención, usando una escala de disfunción global.*
Método: *74 expedientes médicos se escogieron al azar de la población de DDTP de octubre de 1996 a septiembre de 1997, y se examinaron usando un cuestionario de 16 preguntas, basado en el "Addiction Severity Index". La data se procesó y se analizó en el programa Epi Info Versión 6.2. Se aplicó la estadística ji-cuadrado.*
Resultados: *Una mayor retención de pacientes estuvo asociada a las siguientes variables: tener > de 12 años de estudios, ser católico, estar divorciado, vivir con los padres, preferir el uso de más de una sustancia, tener resultados negativos en la toxicología de orina antes y después de tratamiento, al igual que un cambio favorable en la toxicología. Pacientes con problema de uso de sustancia considerable y problemas legales extremos se retuvieron más en tratamiento, al igual que los pacientes sin evidencia de problemas ocupacionales.*
Conclusiones: *La fuerte correlación entre variables específicas y la retención de pacientes en tratamiento por 3 meses o más, debe de alertarnos sobre la importancia de tratamientos accesibles y efectivos en la lucha contra el abuso de sustancias y problemas de salud mental, así como educar e integrar a los familiares en el tratamiento, ya que contar con el apoyo de algún familiar es una de las mejores herramientas que tienen tanto el terapista como el paciente, para ayudarle a mantenerse sobrio.*

References

1. Stark M. J., Campbell B.K., Brinkerhoff C.V. "Hello, May We Help You?" A Study of Attrition Prevention at the Time of the First Phone Contact with Substance-Abusing Clients. Am. J. Drug Alcohol Abuse. Vol 16 Num 1 and 2 1990, pp 67-76.
2. Kleinman P. H., Kang S. Y., Lipton D.S., Woody G.E., Kemp J., Millman R.B. Retention of Cocaine Abusers in Outpatient Psychotherapy. Am. J. Drug Alcohol Abuse. Vol 18 Num 1 1992, pp 29-43.
3. Craig R.J., Olson R.E. Differences in Psychological Need Hierarchy between Program Completers and Dropouts from a Drug Abuse Treatment Program. Am. J. Drug Alcohol Abuse.Vol 14 Num 1 1988, pp 89- 96.
4. Brizer D.A., Maslansky R., Galanter M. Treatment Retention of Patients Referred by Public Assistance to an Alcoholism Clinic. Am. J. Drug Alcohol Abuse. Vol 16 Num 3 and 4 1990, pp 259-264.
5. Bell D.C., Williams M.L., Nelson R., Spence R.T. An Experimental Test of Retention in Residential And Outpatient Programs. Am. J. Drug Alcohol Abuse. Vol 20 Num 3 1994, pp 331-340.
6. Ross H.E., Cutler M., Sklar S.M. Retention in Substance Abuse Treatment. Am. J. Addictions. Vol 6 Num 4 1997, pp 293-303.
7. McCusker J., Bigelow C., Luippold R., Zorn M., Lewis B.F. Outcomes of a 21-Day Drug Detoxification Program: Retention, Transfer to Further Treatment, and HIV Risk Reduction. Am. J. Drug Alcohol Abuse. Vol 21 Num 1 1995, pp 1-16.
8. Conner K.R., Shea R.R., McDermott M.P., Grolling R., Tocco R.V., Baciewicz G. The Role of Multifamily Therapy in Promoting Retention in Treatment of Alcohol and Cocaine Dependence. Am. J. Addictions. Vol 7 Num 1 1997, pp 61-73.
9. Kingree J.B. Understanding Gender Differences in Psychological Functioning and Treatment Retention. Am. J. Drug Alcohol Abuse. Vol 21 Num 2 1995, pp 267-281.
10. Fureman B., Gargi P., Bragg A., Mc Lellan A.T. Addiction Severity Index: A Guide to Training and Supervising ASIS interviews. The University of Pennsylvania ñVeterans Administration Center for Studies of Addiction, april 1990, pp51-119.

Journal Watch:

Deficiencia en el receptor de interleuquina-12 e infecciones severas por salmonella y micobacterias

(Severe mycobacterial and salmonella infections in interleukin-12 receptor-deficient patients)

De Jong, R, Altare, F, Haggen, I-A, et al, Science, 280:1435-1438, 1998
Resumido por Eduardo A. Santiago Delpín, MD

Siempre se ha sospechado que existe una relación causal entre deficiencias de factores inmunológicos específicos y enfermedades infecciosas. Ya ha quedado demostrado, por ejemplo, la asociación de estados de disimunidad con ausencia congénita-genética de poblaciones de células o de algunos factores de crecimiento, al igual que de enfermedades autoinmunes con moléculas individuales o haplotipos del sistema mayor de histocompatibilidad, algunas poblaciones de células T, el receptor de células T y algunos factores supresores.

En este estudio, De Jong y colaboradores -un grupo bastante heterogéneo de investigadores de Holanda y Francia- presentan una asociación como la antes descrita, en pacientes con deficiencia en el receptor de la interleuquina-12 que desarrollan infecciones muy severas con micobacterias y Salmonella.

La interleuquina-12 es una citoquina que promueve la inmunidad celular a patógenos intracelulares mediante la inducción de la célula T ayudante Tipo 1, y la producción de interferón gama. La interleuquina-12 se adhiere a receptores Beta-1 y Beta-2 de alta afinidad, formando complejos en la célula T y en las células asesinas naturales.

Los autores estudiaron tres pacientes no relacionados entre sí, que presentaron infecciones idiopáticas severas por Salmonella paratyphi y Mycobacterium avium; Salmonella Tipo B y Mycobacterium avium intracelulares; y Salmonella typhimium y Mycobacterium bovis. Los autores estudiaron las respuestas a citoquinas Tipo 1, y a células T ayudantes 1, encontrando ausencia del receptor de interleuquina-12 (IL 12-R-B1). Sus células eran deficientes en las señales de interleuquina-12 y en la producción de interferón gama, mientras que las funciones de célula T que preservaban eran todas independientes de interleuquina-12. Ninguno de los tres pacientes demostró deficiencia reconocible o alteraciones en la expresión de las células T, B, NK o macrófagos o sus marcadores de superficie.

Análisis de secuencia demostró mutaciones genéticas que resultaron en codones terminales ubicados prematuramente en el dominio extracelular.

Los tres pacientes pudieron ser tratados exitosamente con antibióticos.

La ausencia de la expresión normal de IL-12 R beta 1 resulta en una inmunodeficiencia humana importante y demuestra el rol esencial de la interleuquina-12 en la resistencia a infecciones secundarias a bacterias intracelulares.

Correspondencia:

POEMA ULTIMO

El coro de voces
es eco, recuerdo
sonoro por siglos
hoy sólo silencio.

El templo vacío
vestigios de incienso
es un espejismo
ceniza en el viento.

Los cirios quemados
su fuego en descenso
su vida una gota
de cera en el suelo.

De aquel crucifijo
más vivo que muerto
la madera rota
podrido su hierro.

Si cierras los ojos
si te quedas quedo
verás los vitrales
oirás el Te Deum
por sólo un momento.
Es eco, es recuerdo.

Eduardo A. Santiago-Delpín, MD



CONTENIDO

Volumen 90

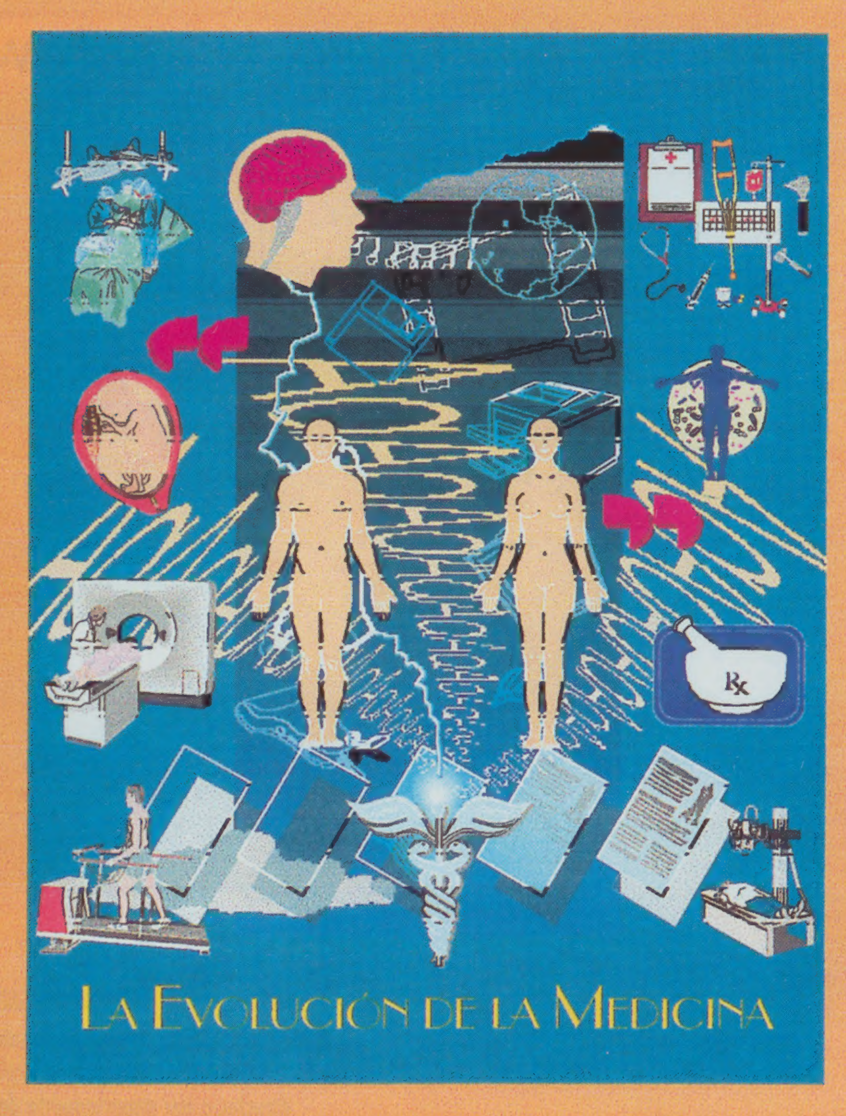
ENERO - FEBRERO - MARZO

ABRIL - MAYO - JUNIO

JULIO - AGOSTO -SEPTIEMBRE - OCTUBRE NOVIEMBRE - DICIEMBRE

INDICE DE AUTORES
VOLUMEN 90

Sociedad Médica Distrito Este
Asociación Médica de Puerto Rico
45ta. Convención Anual



Julio 23-27, 1999

Hotel El Conquistador

Fajardo, Puerto Rico



NATIONAL LIBRARY OF MEDICINE
NLM 01326946 9
Conéctate a
INTERNE
http://www.ssspr.co
RED DE SALUD
Accesa el listado de más de 10,000 médicos, dentistas, laboratorios y hospitales de la red de Triple-S, por localización y especialidad.
SERVICIOS DE SALUD
Consigue información detallada sobre:
▸ productos y servicios de salud de Triple-S
▸ directorio por departamento de la oficina central y teléfonos de las regionales.
REVISTA VITAL
Ponte al día sobre lo último en salud y medicina; haz una conección directa con otras páginas de salud en Internet.
E-MAIL
Solicita información de Triple-S o envía tus comentarios y sugerencias a través del conveniente correo electrónico.
GRUPO CORPORATIVO
Descubre las alternativas que te ofrecen las sub… Triple-S: seguros de vida, incapacidad, propiedad y contingencia, ad… ciamiento de primas.
1870 ABR8 16
05*10*00
MAB
Sometido para aprobación al Comisionado de Seguros de P.R. en 4/15/98.
Trabajando por tu salud... ¡también en Internet!
TRIPLE-S, I